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Cocaine and Alcohol Interactions in Humans: Neuroendocrine Effects and Cocaethylene Metabolism[1]

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ABSTRACT

The effects of 100 mg of intranasal cocaine in acute alcohol intoxication (0.8 g/kg) were evaluated in eight experienced and nondependent healthy volunteers in a double-blind double-dummy, controlled, randomized, crossover clinical study. The combination of alcohol and cocaine produced greater increases in HR, rate-pressure product and pleasurable-related subjective effects (euphoria, well-being) compared with the effects of cocaine. The drug combination reduced the alcohol-induced sedation, but feelings of drunkenness were not significantly counteracted. Cardiovascular changes induced by the combination condition caused an increase in myocardial oxygen consumption that may be related to an increased risk of cardiovascular toxicity. The augmented subjective euphoria may explain why the drug combination is more likely to be abused than is cocaine or alcohol alone. Plasma cortisol concentrations were significantly higher after concomitant alcohol and cocaine use than with cocaine alone. The administration of cocaine did not alter alcohol-induced hyperprolactinemia. Although cocaine produced a slight decrease in plasma concentrations of prolactin when administered alone, it did not antagonize the effects of alcohol on prolactin secretion when alcohol and cocaine were given simultaneously. The combination increased cocaine and norcocaine plasma concentrations, and induced the synthesis of cocaethylene and norcocaethylene. The enhancement of cocaine effects in the drug combination may be due to initially increased cocaine plasma levels followed by the additive effect of cocaethylene, although a pharmacodynamic interaction could not be excluded.

Concurrent ingestion of cocaine and ethanol is an increasingly common presentation (Grant and Hartford, 1990). In a sample of cocaine-dependent patients, more than half of the subjects met criteria for current alcohol dependence, and in more than 50% of the occasions in which cocaine was consumed, both drugs had been used simultaneously (Higgins *et al.*, 1994). In forensic studies, cocaine and ethanol are frequently identified in biological samples from fatally injured drivers (Budd *et al.*, 1989; Marzuk *et al.*, 1990).

Alcohol and cocaine interactions have been extensively investigated in humans. The drug combination produced greater increases in HR and blood pressure than those observed after the use of cocaine alone (Foltin and Fischman, 1989; Farré *et al.*, 1993), reduced the feelings of drunkenness (Higgins *et al.*, 1993), increased cocaine-induced euphoria (Perez-Reyes and Jeffcoat, 1992; Farré *et al.*, 1993; McCance-Katz *et al.*, 1993) and blunted some of the deleterious effects of alcohol on psychomotor performance tasks (Farré *et al.*, 1993; Higgins *et al.*, 1993).

The combined use of cocaine and alcohol increased cocaine and norcocaine plasma levels, reduced benzoylecgonine concentrations and induced the synthesis of cocaethylene. Cocaethylene is an active metabolite of cocaine formed in the presence of ethanol (Farré *et al.*, 1993). The metabolic transformation of cocaine to benzoylecgonine is mediated in part by an hepatic carboxyltransferase, which also transforms cocaine into cocaethylene in the presence of alcohol (Brzezinski *et al.*, 1994). Cocaethylene has been identified in forensic samples (Rafla and Epstein 1979; Jatlow *et al.*, 1991) as well as in urine and blood samples from recreational users of alcohol and cocaine and from healthy volunteers taking part in experimental studies (De la Torre *et al.*, 1991; Perez-Reyes and Jeffcoat, 1992; Farré *et al.*, 1993; McCance-Katz *et al.*, 1993). In humans, the i.v. administration of synthetic coca-

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ABBREVIATIONS: A, amphetamine group; ACTH, adrenocorticotropic hormone; ANOVA, analysis of variance; ARCI, Addiction Research Center Inventory; AUC, area under the curve; BG, benzedrine group; CRF, corticotropin-releasing factor; FPIA, fluorescence polarization immunoassay; HR, heart rate; LSD, lysergic acid dyethylamine group; MBG, morphine-benzedrine group; MEIA, microparticle enzyme immunoassay; PCAG, pentobarbital-chlorpromazine-alcohol group; TRH, thyrotropin-releasing hormone.

ethylene induced lower increases in HR and lower ratings of "high" than cocaine, reaching only 67% and 43% of the magnitude of the respective effects for cocaine (Perez-Reyes *et al.*, 1994), whereas administration (0.95 mg/kg) by the intranasal route produced euphoria and cardiovascular effects similar to those caused by cocaine (0.92 mg/kg) (McCance *et al.*, 1995).

With regard to neuroendocrine actions, the acute administration of alcohol to healthy subjects produced an increase in ACTH (Schuckit *et al.*, 1988) and prolactin plasma levels (Schuckit *et al.*, 1987a). In some studies, alcohol increased plasma cortisol levels, though others found no changes (Camí *et al.*, 1988; Inder *et al.*, 1995). The acute administration of cocaine induced an increase in ACTH and corticosterone levels in rats (Rivier and Vale, 1987; Borowsky and Kuhn, 1991; Levy *et al.*, 1991; Torres and Rivier, 1992) and monkeys (Sarnyai *et al.*, 1996). In humans, cocaine administration increased ACTH levels in cocaine-dependent subjects (Mendelson *et al.*, 1992a; Teoh *et al.*, 1994), and an increase in cortisol levels has been described in i.v. cocaine abusers (Baumann *et al.*, 1995). Although a decrease in plasma prolactin concentrations has been documented in rhesus monkeys after the acute administration of cocaine (Mello *et al.*, 1990a, 1990b, 1993), this inhibitory effect was not found in cocaine-dependent humans or i.v. cocaine abusers as compared with placebo (Mendelson *et al.*, 1992a; Baumann *et al.*, 1995). Hyperprolactinemia, however, has been described in cocaine-dependent subjects and explained in relation to a dopaminergic impairment (Mendelson *et al.*, 1988; Mendelson *et al.*, 1989).

This study was conducted to assess complementary aspects of a previous study on alcohol and cocaine interactions in healthy volunteers (Farré *et al.*, 1993), in particular the effects of the combined use of cocaine and alcohol on neuroendocrine regulation, and to obtain further information on the metabolic pathway of cocaethylene. Subjective, cardiovascular and pharmacokinetic effects were also evaluated.

Materials and Methods

Subjects. Subjects were recruited "by word of mouth." Eligibility criteria required the recreational use of cocaine by the intranasal route on at least six occasions during the 3 months before participation in the study, a minimum daily alcohol consumption of 30 g and previous experiences in acute alcohol intoxication.

Eight healthy male volunteers were selected and paid for their participation in the study. Mean age, body weight and height were 27 years (range 25–30), 69.6 kg (range 64.0–77.6) and 176 cm (range 161–184), respectively. Their average consumption of alcohol was 44 g/day, and their average use of cocaine by the intranasal route was between once and twice per month in the previous year. All but three subjects were smokers. None had a history of abuse or drug dependence according to DSM III-R criteria (American Psychiatric Association, 1987). Subjects were informed that they would receive cocaine, alcohol and/or placebo in different combinations. Each subject underwent a medical examination, including ECG, and a routine laboratory screening and signed an informed consent. The study was approved by the institutional Review Board and was authorized by the Ministry of Health ("Dirección General de Farmacia y Productos Sanitarios" 93/80).

Study design. Subjects participated as outpatients in seven 8-hr experimental sessions in which the same doses and preparations of cocaine and alcohol were used. In each session, they drank a beverage containing alcohol or its placebo and snorted a powder containing cocaine or its placebo. Subjects arrived at the laboratory at 10:45 A.M. after an overnight fast and had an indwelling i.v. catheter inserted into a vein in the forearm of the nondominant arm. Thereafter, they remained seated in a quiet room throughout the session. Drug administration started around 12:00 A.M.. Three hours after drug administration, subjects had a light meal. Brief visits to the bathroom and tobacco smoking were permitted 3 hr after drug administration.

Three training sessions were carried out to familiarize the volunteers with testing procedures and to assess their tolerability to the drugs. During the first session, they received both placebos; in the following two sessions, cocaine and alcohol were given at random and in a double-blind double-dummy fashion. Results from the training sessions are not described here.

Four study sessions were carried out during which different combinations of drugs were given in a double-blind double-dummy fashion. Combinations were as follows: alcohol p.o./placebo snorted (alcohol condition), placebo p.o./cocaine snorted (cocaine condition), alcohol p.o./cocaine snorted (drug combination condition), and placebo p.o./placebo snorted (placebo condition). The sequences of treatment were randomized using a 4×4 Latin square crossover design. Sessions were separated by a washout period of at least 72 hr.

Drugs. Acute alcohol intoxication was induced by the ingestion of vodka (Stolichnaya red label) and tonic water containing a total alcohol dose of 0.8 g/kg. Several drops of aromatic bitters and lemon juice were added to mask the placebo drink, which contained tonic water only (Camí *et al.*, 1988; Farré *et al.*, 1993). The total volume of liquid was 450 ml. Subjects were given 30 min to consume the beverage, drinking 150 ml every 10 min.

Cocaine hydrochloride (pharmaceutical grade) was provided by the Ministry of Health. Cocaine HCl in doses of 100 or 5 mg was mixed with lactose to obtain a total 200 mg of powder for administration. The 5-mg cocaine preparation was used as placebo, because it has been reported that at these doses, blood cocaine levels are insignificant and subjective or cardiovascular effects are absent, although a slight numbing sensation is produced in the nasal mucosa (Javaid *et al.*, 1978). Subjects received the powder on a steel plate measuring 30×15 cm and prepared their own two "lines" using a straight-edge razor. They snorted the powder using a straw, one "line" for each nostril, immediately after the last drink (30 min after the start of beverage administration).

Cardiovascular effects. Noninvasive HR and blood pressure were recorded at −30, 0 (immediately before beverage administration), 15, 28 (before powder snorting), 35, 40, 45, 50, 55, 60, 67, 75, 82, 90, 97, 105, 112, 120, 150, 180, 210, 270, 390 and 1470 min using a Dinamap 8100-T vital signs monitor (Critikon, Tampa, FL). For safety reasons, ECG, oral temperature and pulse oxymetry were continuously monitored during the first 3 hr of the session using a Dinamap Plus vital signs monitor (Critikon).

Subjective effects. Subjective effects were measured using the ARCI questionnaire and a set of 13 different visual analog scales. ARCI is a true-false questionnaire with empirically derived scales that are sensitive to the effects of a variety of classes of drugs of abuse (Haertzen, 1974). We used a short form of the inventory that consists of five scales with a total of 49 items (Martin *et al.*, 1971). A Spanish validated version (Lamas *et al.*, 1994) was administered. The five scales were PCAG (a measure of sedation), MBG (a measure of euphoria), LSD (a measure of dysphoria and somatic symptoms), BG (a stimulant scale consisting mainly of items related to intellectual efficiency and energy) and A (an empirically derived scale sensitive to the effects of *d*-amphetamine). ARCI was administered at 0 (immediately before beverage administration), 45, 90 and 390 min after drug administration.

A total of 13 visual analog scales (100 mm) labeled with different adjectives marked at opposite ends with "not at all" and "extremely" were used. Subjects rated effects as "high," "drunk," "any effect," "good effects," "bad effects," "liking," "feeling good," "clear-headed," "content," "better performance," "worse performance," "hungry" and "drowsy." The visual analog scales were administered at 0 (before

beverage administration), 15, 28, 30 (immediately after powder snorting), 35, 40, 45, 50, 55, 60, 67, 75, 82, 90, 97, 105, 120, 150, 180, 210, 270 and 390 min.

Blood sampling. An indwelling i.v. catheter was inserted in a peripheral vein, and 0.9% sodium chloride solution was infused at a rate of 20 ml/hr. Blood samples (2 ml) were obtained for cortisol and prolactin analysis at 0, 40, 50, 60, 75, 90, 120 and 180 min after beverage administration. Samples were collected in chilled tubes and centrifuged immediately for 5 min at 3000 rpm at −4°C. The serum was removed and frozen at −20°C until analysis.

Blood samples (2 ml) were obtained for analysis of alcohol at 0, 15, 28, 40, 50, 60, 75, 90, 120, 180, 270 and 390 min after beverage administration. The whole blood was collected in a plastic chilled tube over 25 μl of sodium heparin, and 1 ml was transferred to a vial containing 1 ml of water and 100 μl of *tert*-butyl alcohol.

Blood samples (4 ml) for the analysis of cocaine, benzoylecgonine, ecgoninemethylester, norcocaine, cocaethylene and norcocaethylene were also obtained at 0, 40, 50, 60, 75, 90, 105, 120, 150, 180, 210, 270 and 390 min after beverage administration (or −30, 10, 20, 30, 45, 60, 75, 90, 120, 150, 180, 240 and 360 min after powder snorting). Samples were collected in tubes containing 100 μl of citric acid and 200 μl of a saturated solution of sodium fluoride as enzymatic inhibitor and chilled until centrifugation (Baselt, 1983; Isenschmid *et al.*, 1989). Plasma samples were separated and stored at −20°C until analysis.

Hormone analysis. Plasma cortisol concentrations were determined by FPIA (Abbott Laboratories, Chicago, IL) according to the manufacturer's instructions. A good correlation between FPIA results and reference methods has previously been shown (Kobayashi *et al.*, 1979). The intra-assay coefficients of variation (CV) were 2.92% (± 0.10), 7.78% (± 1.08) and 2.60% (± 0.96), for low (4.00 μg/dl), medium (15.00 μg/dl) and high (40.00 μg/dl) controls. Inter-assay CV were 17.43% (± 0.70), 10.31% (± 1.52) and 4.74% (± 1.81), respectively. The assay sensitivity is reported to be 0.45 μg/dl.

We determined prolactin plasma levels by MEIA (Abbott Laboratories, Chicago, IL), using an IMx instrument and following the manufacturer's instructions. A good correlation between MEIA results and reference methods has previously been shown (Bodner *et al.*, 1991). The MEIA assay sensitivity is reported to be 0.6 ng/ml. Intra-assay CV were 1.61% (± 0.12), 1.41% (± 0.26), and 1.02% (± 0.40) for low (8.00 ng/ml), medium (20.00 ng/ml) and high (40.00 ng/ml) controls. Inter-assay CV were 3.56% (± 0.27), 3.79% (± 0.71) and 5.39% (± 2.05), respectively. The IMx prolactin calibrators have been assigned values relative to the World Health Organization 2nd International Standard (WHO 2nd IS 83/562), where 1 ng/ml is equivalent to 24 mIU/l.

Drug and metabolite analyses. Blood alcohol levels were measured by gas-liquid chromatography (HP 5890 Hewlett-Packard, Palo Alto, CA) using a head-space injection technique (HP 19395A) and flame ionization detection. Separation was carried out using a cross-linked capillary column (RSL-160 Alltech, Deerfield, IL) 5 m long × 0.53 mm I.D. (film thickness 0.33 μm) (Farré *et al.*, 1993). The method showed a good linearity (area ratio of the internal standard *vs.* concentration) from 50.6 to 1264.0 μg/ml (r = 0.9977, intercept = 0.053, slope = 0.0015). Intra-assay and inter-assay coefficients of variation for low concentrations were 7.8% and 10.3%, and for high concentrations were 0.9% and 3.3%, respectively.

Blood levels of cocaine, benzoylecgonine, ecgoninemethylester, norcocaine, cocaethylene and norcocaethylene were determined by gas chromatography coupled with mass spectrometry. A gas chromatograph (HP 5890 Series II) fitted with an autosampler (HP 7673A) was coupled to a mass selective detector (HP 5970). Separation was carried out using a cross-linked capillary column (Ultra2-HP) 25 m long × 0.2 mm I.D., 5% phenyl-methyl silicone gum (film thickness 0.33 μm). The mass spectrometer was operated by electron impact ionization (70 eV) and in the single-ion monitoring acquisition mode. Samples were prepared by a single clean-up step by reversed solid-phase with cationic exchange extraction using as internal standards deuterated analogs of cocaine and its metabolites. The residues were derivatized, dried and redissolved in 50 μl of ethyl acetate, and 2 μl was injected into the chromatographic system (De la Torre *et al.*, 1995). Good linearity (area ratio of the internal standard *vs.* concentration) was obtained over the ranges studied (cocaine: 50–600 ng/ml, r = 0.9993, intercept = −0.0074, slope = 0.0042; benzylecgonine: 50–1000 ng/ml, r = 0.9985, intercept = 0.0110, slope = 0.0041; ecgoninemethylester: 20–400 ng/ml, r = 0.9963, intercept = 0.0448, slope = 0.0039; norcocaine: 1–15 ng/ml, r = 0.9961, intercept = 0.0070, slope = 0.0515; cocaethylene: 10–150 ng/ml, r = 0.9954, intercept = −0.0024, slope = 0.0119; norcocaethylene: 1–15 ng/ml, r = 0.9980, intercept = 0.0251, slope = 0.0722). Recoveries (mean ± S.D.) were 98.0 ± 2.0% for cocaine, 80.1 ± 2.4% for benzoylecgonine, 81.7 ± 5.0% for ecgoninemethylester, 78.8 ± 9.6% for norcocaine, 97.1 ± 1.7% for cocaethylene and 71.8 ± 18.8% for norcocaethylene. Intra-assay coefficients of variation (50 ng/ml for cocaine and benzoylecgonine; 20 ng/ml for ecgoninemethylester; 1 ng/ml for norcocaine and norcocaethylene; 10 ng/ml for cocaethylene) ranged between 4.2% for benzoylecgonine and 10.1% for ecgoninemethylester. Inter-assay coefficients of variation (100 ng/ml for cocaine and benzoylecgonine; 50 ng/ml for ecgoninemethylester; 2 ng/ml for norcocaine and norcocaethylene; 20 ng/ml for cocaethylene) ranged between 4.2% for benzoylecgonine and 12.6% for norcocaine.

Data analysis. Values from cardiovascular variables (including the rate-pressure product; Gobel *et al.*, 1978), subjective variables and hormone concentrations were transformed to differences from base-line measures. The peak effect (maximum absolute change from base-line values) and the 3-hr AUC of effects *vs.* time calculated by the trapezoidal rule were determined for each variable except ARCI scores, which were evaluated only as peak effects. These transformations were analyzed by a one-factor repeated-measures ANOVA with drug condition as factor. When ANOVA results showed significant differences between treatment conditions, *post-hoc* multiple comparisons were performed using the Tukey test. Differences associated with P values lower than .05 were considered significant.

With regard to plasma concentrations of alcohol and cocaine, the following parameters were calculated: peak concentration (C_{max}), time taken to reach peak concentration (T_{max}), area under the concentration-time curve from 0 to 360 or 390 min (AUC_{0-390} for alcohol; AUC_{0-360} for cocaine and its metabolites). AUC values were calculated by the trapezoidal rule. The paired Student's t test was used for statistical analysis. Results were considered statistically significant at $P < .05$.

Results

HR and blood pressure. Cardiovascular effects after the administration of placebo, alcohol, cocaine and the drug combination are shown in table 1 and figure 1. Either alcohol or cocaine and the drug combination produced an increase in HR compared with placebo when the peak effects were considered, whereas for the AUC of pulse rate *vs.* time, only the drug combination increased the HR compared with placebo. The drug combination produced an increase in peak HR and in AUC of HR *vs.* time in comparison with either alcohol and cocaine. The peak difference between the conditions of alcohol and placebo was 17 bpm, between cocaine and placebo was 23 bpm and between placebo and the drug combination was 41 bpm. The difference between alcohol and the drug combination was 24 bpm, and that between cocaine and the drug combination was 18 bpm.

Systolic blood pressure did not show statistically significant differences when the four conditions were compared by means of the Tukey test, although both conditions that included cocaine showed increased peak differences (10 mm Hg) as compared with placebo. Alcohol decreased diastolic

TABLE 1

Statistical results of cardiovascular measures, subjective effects and hormone plasma levels

Variable	ANOVA (DF 3, 21)		Tukey Multiple-Comparison Tests					
			Placebo			Alcohol		Cocaine
	F	P value	Alc	Coc	Alc/Coc	Coc	Alc/Coc	Alc/Coc
Cardiovascular Measures								
HR								
AUC	14.35	<.0001	N.S.	N.S.	**	N.S.	**	**
Peak	22.62	<.0001	*	**	**	N.S.	**	**
SBP								
AUC	3.41	.0364	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.
Peak	1.17	.3458						
DBP								
AUC	11.91	.0001	*	N.S.	N.S.	**	**	N.S.
Peak	16.74	<.0001	*	N.S.	*	**	**	N.S.
ARCI								
PCAG								
Peak	20.52	<.0001	**	N.S.	**	**	**	N.S.
MBG								
Peak	9.66	.0030	N.S.	N.S.	**	N.S.	**	N.S.
LSD								
Peak	2.87	.0608						
BG								
Peak	15.57	<.0001	N.S.	N.S.	**	*	**	*
A								
Peak	24.85	<.0001	N.S.	**	**	*	**	**
Visual Analog Scales								
High								
AUC	32.52	<.0001	N.S.	*	**	*	**	**
Peak	31.35	<.0001	N.S.	**	**	**	**	N.S.
Drunk								
AUC	15.25	<.0001	**	N.S.	*	**	N.S.	*
Peak	20.42	<.0001	**	N.S.	**	**	N.S.	**
Any effect								
AUC	13.80	<.0001	**	N.S.	**	N.S.	N.S.	**
Peak	12.39	.0001	**	**	**	N.S.	N.S.	N.S.
Good effects								
AUC	10.77	.0002	N.S.	N.S.	**	N.S.	*	**
Peak	12.89	.0001	**	**	**	N.S.	**	N.S.
Bad effects								
AUC	7.28	.0016	**	N.S.	N.S.	**	N.S.	N.S.
Peak	12.34	.0001	**	N.S.	**	**	N.S.	*
Liking								
AUC	6.29	.0033	N.S.	N.S.	**	N.S.	N.S.	*
Peak	9.34	.0004	N.S.	**	**	N.S.	N.S.	N.S.
Feeling good								
AUC	7.70	.0012	N.S.	N.S.	**	N.S.	*	*
Peak	12.11	.0001	*	**	**	N.S.	*	N.S.
Clear-headed								
AUC	9.58	.0003	N.S.	N.S.	**	N.S.	**	*
Peak	13.45	<.0001	N.S.	**	**	N.S.	**	N.S.
Content								
AUC	7.19	.0017	N.S.	N.S.	**	N.S.	N.S.	*
Peak	10.81	.0002	**	*	**	N.S.	N.S.	N.S.
Better performance								
AUC	10.59	.0002	N.S.	N.S.	**	N.S.	**	**
Peak	12.24	.0001	N.S.	*	**	N.S.	**	N.S.
Worse performance								
AUC	2.86	.0611						
Peak	3.53	.0324	*	N.S.	N.S.	N.S.	N.S.	N.S.
Hungry								
AUC	2.27	.1103						
Peak	2.94	.0569						
Drowsy								
AUC	5.08	.0084	N.S.	N.S.	N.S.	**	*	N.S.
Peak	7.52	.0013	N.S.	N.S.	N.S.	**	*	N.S.
Hormones								
Cortisol								
AUC	35.74	<.0001	N.S.	**	**	**	**	*
Peak	48.16	<.0001	N.S.	**	**	**	**	*
Prolactin								
AUC	4.32	.0160	N.S.	N.S.	N.S.	**	N.S.	**
Peak	9.86	.0003	*	N.S.	*	**	N.S.	**

Abbreviations: Alc, alcohol; Coc, cocaine; Alc/Coc, alcohol-cocaine combination; AUC, area under the curve from 0 to 180 min; SBP, systolic blood pressure; DBP, diastolic blood pressure; *F*, ANOVA's *F* value (DF 3, 21); P, statistical significance level. Tukey test statistical significance: * $P < .05$; ** $P < .01$. N.S. = non significant. A blank indicates not done (ANOVA not significant).

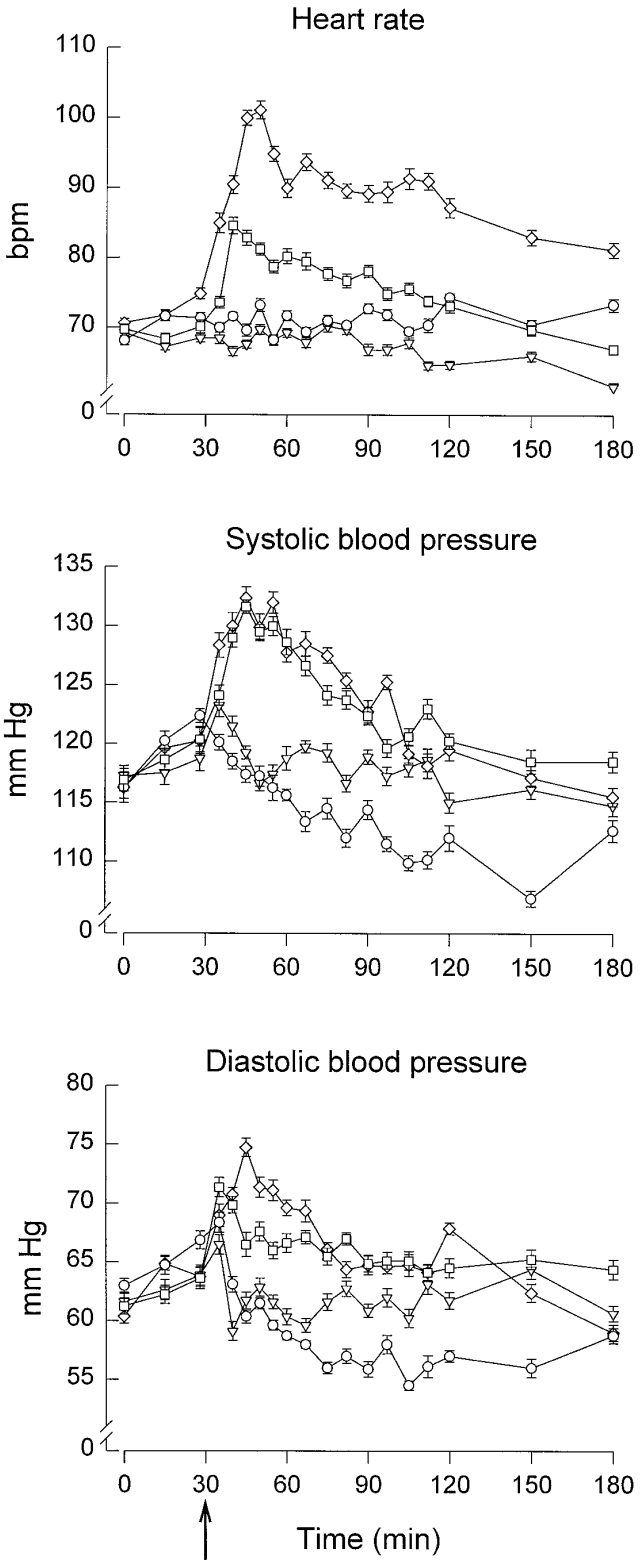

Fig. 1. Time course (mean ± S.E.M., n = 8) of HR, systolic blood pressure and diastolic blood pressure after administration of placebo (▽), alcohol (○), cocaine (□) and the combination of alcohol and cocaine (◇). The arrow signals cocaine administration.

blood pressure as compared with placebo when either peak effects or AUC of effects was considered. The drug combination produced an increase in diastolic blood pressure in comparison with placebo only for AUC. Both conditions that included cocaine increased peak differences and AUC of diastolic blood pressure as compared with alcohol. The peak difference in diastolic blood pressure between alcohol and placebo conditions was −14 mm Hg, between cocaine and placebo conditions was 11.5 mm Hg and between placebo and the drug combination conditions was 12 mm Hg. The peak difference in diastolic blood pressure in comparison with alcohol was 25.5 mm Hg for cocaine and 26 mm Hg for the drug combination.

Results for the rate-pressure product (calculated as systolic blood pressure times HR) were as follows: drug combination (peak 5244; AUC 396,916) produced a significant increase compared with placebo (peak −1,193; AUC −50,488), alcohol (peak 918; AUC 33,158) and cocaine (AUC 148,257). Cocaine increased peak values in comparison with placebo (2,827 *vs.* −1,193).

Subjective effects. Alcohol increased peak PCAG score of the ARCI questionnaire as compared with placebo and with both conditions that included cocaine. The drug combination decreased peak PCAG score as compared with placebo and increased MBG score as compared with either placebo or alcohol. No differences between drug conditions were found in the LSD scores. Cocaine increased BG score as compared with alcohol. The drug combination increased BG and A scores as compared with all three other conditions, and cocaine increased A score as compared with either placebo or alcohol.

Increases in the ratings of drunk, any effect, good effects (peak), bad effects, feeling good (peak), content (peak) and worse performance (peak) were found when alcohol was given as compared with placebo. Cocaine produced increases in the ratings of high, any effect (peak), good effects (peak), liking (peak), feeling good (peak), clear-headed (peak), content (peak) and better performance (peak) in comparison with placebo. The combination condition increased the ratings of high, drunk, any effect, good effects, bad effects (peak), liking, feeling good, clear-headed, content and better performance as compared with placebo. The combination condition produced higher ratings than alcohol in the scales of high, good effects, feeling good, clear-headed and better performance. Ratings for the drug combination condition were higher as compared with cocaine in the scales of high (AUC), drunk, any effect (AUC), good effects (AUC), bad effects (peak), liking (AUC), feeling good (AUC), clear-headed (AUC), content (AUC) and better performance (AUC).

The subjective effects increased to maximal between 30 and 45 min after cocaine administration (60 to 75 min when considering alcohol administration), then fell slowly and finally vanished between 180 and 240 min after drug administration (cocaine administration) (fig. 2).

Subjective effects after the administration of placebo, alcohol, cocaine and the drug combination are shown in table 1 and figures 2 (time course of high and liking visual analog scales), 3 (peaks of ARCI questionnaire) and 4 (peaks of visual analog scales).

Cortisol. Plasma cortisol concentrations were significantly higher (peak and AUC) after the administration of both conditions that included cocaine as compared with either placebo or alcohol. The combination condition produced a significantly higher increase in cortisol concentrations than did cocaine alone. Cortisol concentrations peaked 60 min after cocaine administration in the cocaine condition (90 min

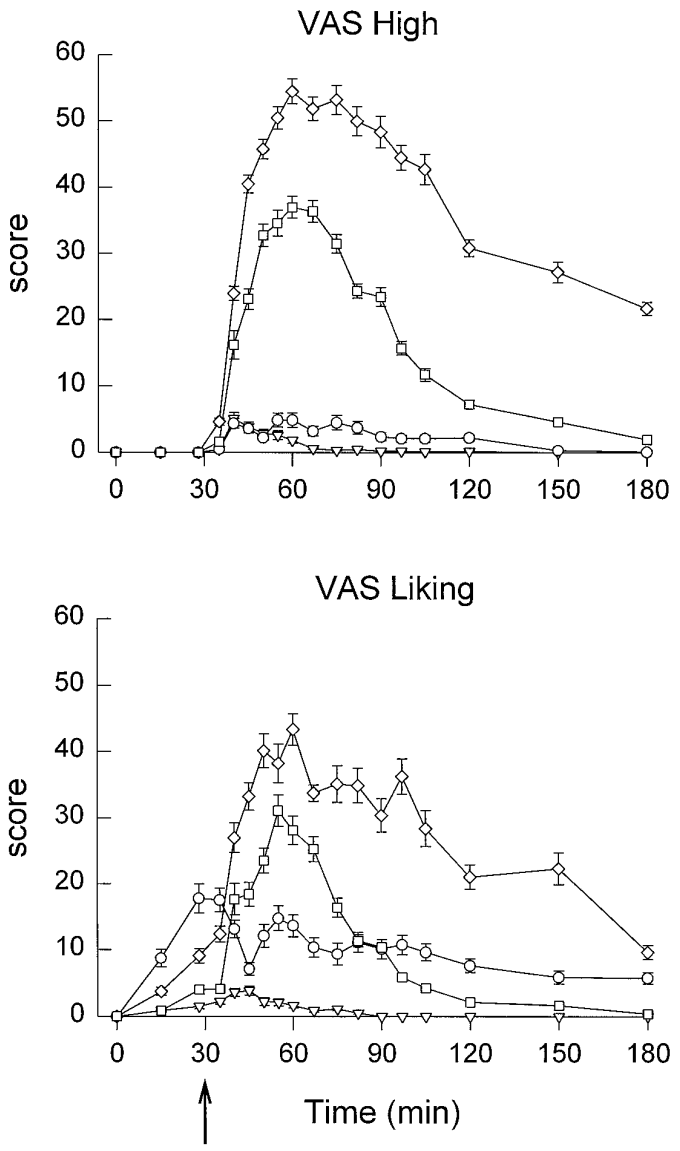

Fig. 2. Time course (mean ± S.E.M., $n = 8$) of high and liking visual analog scales scores. Other details of the figure are similar to those for figure 1.

after alcohol administration), whereas in the combination condition, peak effects occurred 15 min earlier, 45 min after cocaine administration (75 min after alcohol ingestion). At 210 min after cocaine administration, cortisol concentrations were similar in the four treatment conditions. The mean peak difference in the plasma cortisol concentration between cocaine and placebo conditions was 10 μg/dl, and between cocaine and alcohol conditions was 9 μg/dl. The differences between the drug combination and placebo and between the drug combination and alcohol were 15 μg/dl and 14 μg/dl respectively. The difference between the drug combination and cocaine condition was 5 μg/dl. The effects of all treatment conditions on plasma cortisol levels are shown in table 1 and figure 5.

Prolactin. Prolactin plasma concentrations were increased after the administration of both conditions that included alcohol as compared with placebo (AUC) and cocaine (AUC and peak) conditions. No differences were found between alcohol and combination conditions. Placebo induced a slight decrease in plasma prolactin concentrations. After cocaine administration, plasma prolactin levels also decreased and remained below those achieved with placebo throughout the study period, although statistically significant differences were not reached. Prolactinemia peaked in both conditions that included alcohol 40 min after the beginning of alcohol drinking (10 min after beverage ending). The nadir concentrations were observed 90 min after cocaine administration and 120 min after placebo administration. Two hours after alcohol administration, prolactin concentrations were similar among all treatment conditions. The mean peak difference in prolactin plasma concentration between alcohol and placebo conditions was 6 ng/ml, and between alcohol and cocaine conditions was 8 ng/ml. The differences between the drug combination and placebo and between the drug combination and cocaine were 5 ng/ml and 8 ng/ml respectively. The peak difference between alcohol and drug combination conditions was negligible. The effects of all treatment conditions on plasma prolactine concentrations are shown in table 1 and figure 5.

Pharmacokinetic data. When the two conditions that included alcohol were compared, no significant differences were found in the pharmacokinetic parameters, except for C_{max} in the alcohol-alone condition (table 2).

Plasma levels of cocaine in the drug combination condition were higher than in the cocaine condition as reflected by significantly greater values of C_{max} and AUC_{0-360}. Plasma levels of benzoylecgonine were significantly higher in the cocaine condition than in the drug combination condition as reflected by C_{max} and AUC_{0-360}. None of the pharmacokinetic parameters derived from ecgoninemethylester plasma levels showed significant differences. Plasma levels of norcocaine in the drug combination condition were higher than in the cocaine condition as reflected by AUC_{0-360}. Cocaethylene and norcocaethylene were detected only in the combination group.

The pharmacokinetic parameters for cocaine and its metabolites are shown in table 2. The time courses of mean plasma levels of cocaine, benzoylecgonine, ecgoninemethylester, norcocaine, cocaethylene and norcocaethylene are shown in figures 6 to 8.

Discussion

This study shows the increased pharmacological effects of cocaine and alcohol coadministration compared with the effects of both drugs given separately, a finding that confirms previous observations reported by our group (Farré *et al.*, 1993) and by other authors (Perez-Reyes and Jeffcoat, 1992; Higgins *et al.*, 1993; McCance-Katz *et al.*, 1993). However, as far as we know, this is the first study in which the effects of both drugs on plasma concentrations of cortisol and prolactin have been examined in humans.

The alcohol dose (0.8 g/kg) used in this study produced a characteristic increase in the scores of drunkenness and sedation (ARCI-PCAG scale) as well as increases in HR and decreases in diastolic blood pressure as compared with placebo. These results are in agreement with the study of Higgins *et al.* (1993), who used a dose of alcohol of 1 g/kg. The intranasal administration of 100 mg of cocaine also reproduced the previously reported effects on subjective and cardiovascular variables (Resnick *et al.*, 1976; Farré *et al.*, 1993):

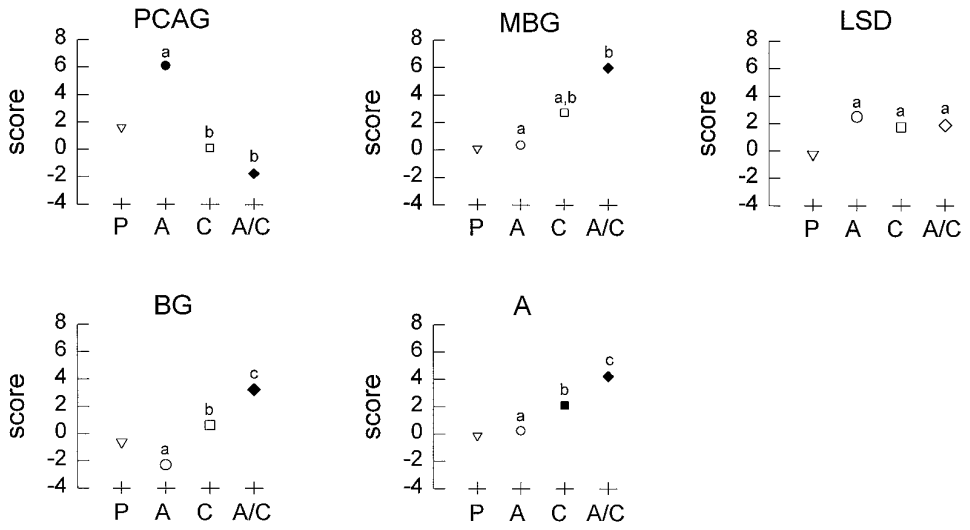

Fig. 3. Peak effects (mean, $n = 8$) on ARCI scales after administration of placebo (▽, P), alcohol (○, A), cocaine (□, C) and the combination of alcohol and cocaine (◇, A/C). Filled symbols indicate a significant difference from placebo ($P < .05$). The letters a, b, and c indicate comparisons among the three active drug conditions; within the same panel, any two means designated with the same letter are not significantly different from each other at $P < .05$ (Tukey's *post-hoc* tests).

increases in HR, diastolic blood pressure and subjective effects related to euphoria, well-being and central activation ("high," "good effects," "feeling good" and ARCI-A scale). Cocaine produced an increase in the scores on the MBG scale as compared with placebo but these differences were not statistically significant when intranasal cocaine was given. Only the i.v. administration of cocaine induced significant increases in scores on the MBG scale (Foltin and Fischman, 1991).

The combination of alcohol and cocaine produced a significant increase in the HR when compared with placebo, alcohol alone and cocaine alone. The increase in diastolic blood pressure was statistically significant when compared with placebo and with alcohol. These findings have been also observed in healthy volunteers by others (Foltin and Fischman, 1989; Perez-Reyes and Jeffcoat, 1992; Higgins *et al.*, 1993; McCance-Katz *et al.*, 1993). The elevations in HR and blood pressure with the drug combination result in increased myocardial oxygen consumption (measured by the rate-pressure product), which may be responsible for the observed increased risk of cardiovascular complications seen in those who use both cocaine and alcohol. However, in the study of Pirwitz *et al.* (1995), an increase in myocardial oxygen consumption was accompanied by coronary vasodilation when cocaine and i.v. ethanol were given concomitantly, whereas coronary vasoconstriction was observed after the use of intranasal cocaine alone.

The simultaneous use of alcohol and cocaine produced more marked subjective effects than alcohol or cocaine alone. Sedation ratings were lower than after alcohol administration (PCAG or "drowsy" scores) and were even lower than after placebo (PCAG scores). Drunkenness scores were reduced when cocaine was administered after alcohol, but these differences were not statistically significant. In our previous study, a similar result was obtained with 100 mg of cocaine and 1 g/kg of alcohol (Farré *et al.*, 1993). In the study of Higgins *et al.* (1993), in which 96 mg of cocaine was given together with 1 g/kg of alcohol, alcohol-induced feelings of intoxication were significantly reduced by the stimulant drug. This difference may be explained by a lack of statistical power for this variable ($1 - \beta = 0.69$ for this comparison).

The drug combination was followed by higher ratings on the MBG scale, an objective measure of drug-induced euphoria (Martin *et al.*, 1971), as compared with placebo and alcohol, but the difference between the two conditions that included cocaine was not statistically significant. The drug combination also raised the ratings of the BG and A scales in comparison with the other drug conditions. These effects have previously been described with the use of cocaine or other stimulant agents (Martin *et al.*, 1971). Compared with cocaine alone, the drug combination also produced a generalized increase in self-reported subjective effects when AUC differences were considered, but not when peak differences were analyzed. This could be due to the longer duration of effects when alcohol and cocaine are given concurrently. Higher scores in all the visual analog scales except "worse performance," "hungry" and "drowsy" were found after the drug combination than after the administration of cocaine alone. These results are consistent with other reports (Higgins *et al.*, 1993; McCance-Katz *et al.*, 1993; Farré *et al.*, 1993), but an enhancement in the scale "high" after cocaine and alcohol administration was found in one study only (Perez-Reyes and Jeffcoat, 1992). Taking into account the subjective profile we have cited, it seems that the drug combination produces more pleasurable effects, and this may explain why the drug combination is more likely to be abused than alcohol or cocaine alone.

With regard to the neuroendocrine effects of the testing conditions, one novel aspect of the study, the administration of ethanol (0.8 g/kg) was not followed by an increase in plasma cortisol concentrations. The effects of different doses of alcohol on the hypothalamic-pituitary-adrenal axis have been investigated extensively in experimental models. In rats, alcohol induced the release of CRF, ACTH and corticosterone. Alcohol perfusion on incubated hypothalami caused the release of CRF (Redei *et al.*, 1988). Alcohol seems to have direct action on hypothalamic centers, but other regions must also be implicated in the response, because the alcohol-induced secretion of ACTH was partially attenuated, but not completely abolished, by lesions of the paraventricular nucleus or after inmunoneutralization of endogenous CRF (Rivest and Rivier, 1994). In humans, however, the effects of alcohol on the release of ACTH are conflicting: increases in ACTH levels have been found after the administration of alcohol at doses of 0.695 g/kg (Lukas and Mendelson, 1988) and 1.1 g/kg (Schuckit *et al.*, 1988), and no increase at all has been found with doses between 0.75 and 1.3 g/kg (Ida *et al.*, 1992; Waltman *et al.*, 1993; Inder *et al.*, 1995). On the other

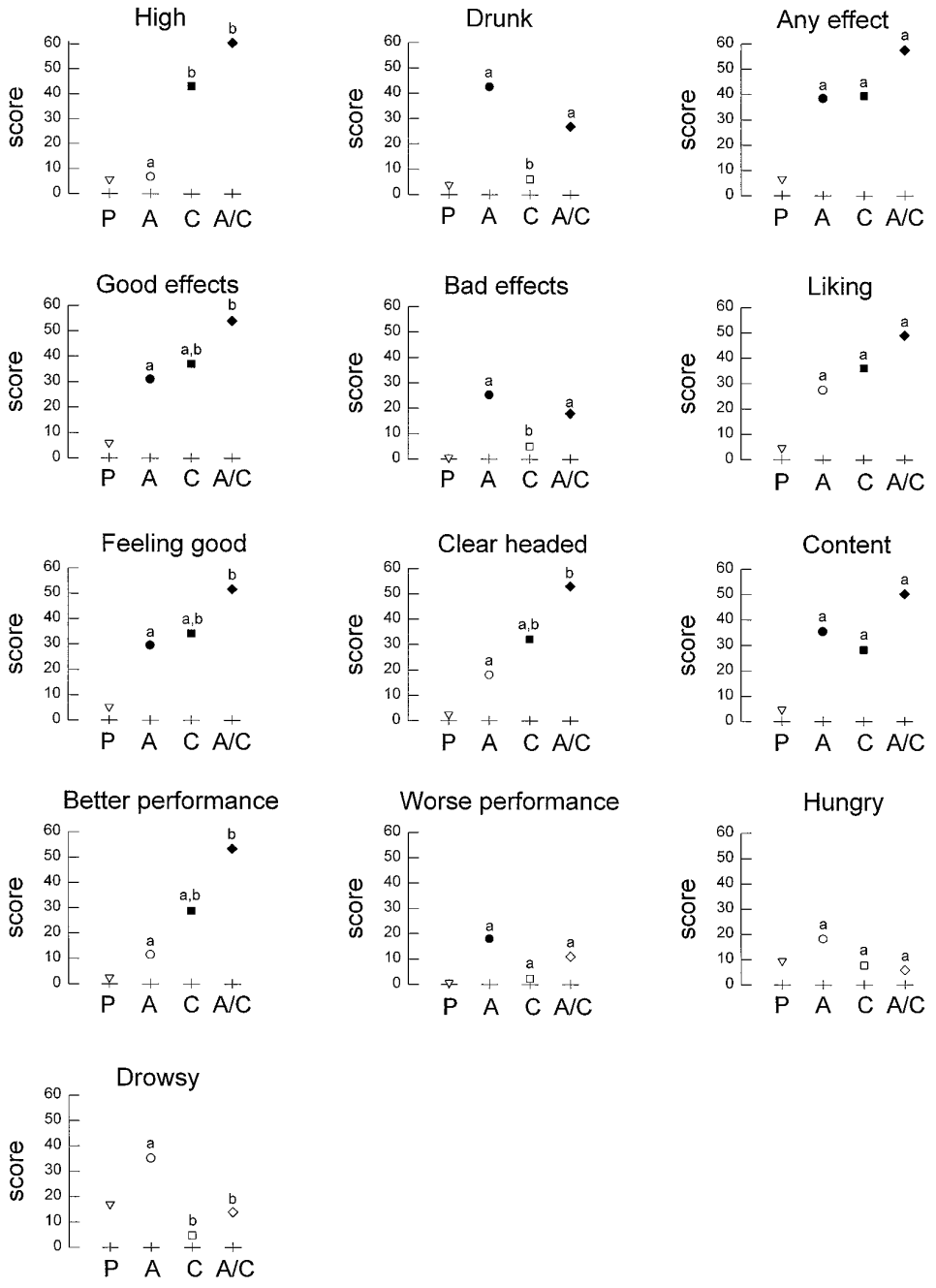

Fig. 4. Peak effects (mean, $n = 8$) on visual analog scales. Other details of the figure are similar to those for figure 3.

hand, elevations of cortisol concentrations in serum that seemed directly related to plasma levels of alcohol were described after the administration of 1.1 g/kg (Schuckit *et al.*, 1987b; Lukas and Mendelson, 1988). Although a threshold of blood alcohol concentration of 100 mg/dl has been suggested to cause elevations of cortisol (Jenkins and Connolly, 1968), other studies have not been able to show an increase even after ethanol blood levels higher than this threshold (Ida *et al.*, 1992; Waltman *et al.*, 1993). Interestingly, the administration of alcohol attenuated naloxone-induced hypercortisolemia (Camí *et al.*, 1988) and blunted the ovine corticotropin-releasing hormone-stimulated ACTH release in healthy volunteers (Waltman *et al.*, 1993). It has been suggested that cortisol increases might appear only in subjects with gastrointestinal symptoms related to alcohol intolerance, such as nausea and vomiting (Inder *et al.*, 1995). None of the subjects in our study had digestive complaints.

In healthy volunteers, the intranasal use of cocaine was followed by a marked increase in cortisol plasma levels. As far as we know, the results of cocaine in this population setting have not been previously reported. This finding is consistent with previous observations in animal models in which cocaine induced a release of CRF, ACTH, β-endorphin and corticosterone (Rivier and Vale, 1987; Borowsky and Kuhn, 1991; Levy *et al.*, 1991; Torres and Rivier, 1992; Sarnyai *et al.*, 1996). The increase in ACTH secretion seems to be mediated by CRF release. It has been shown that cocaine-stimulated ACTH and corticosterone release are blunted by peripheral and i.c.v. administration of both CRF antiserum and a CRF receptor antagonist (Rivier and Vale, 1987; Sarn-

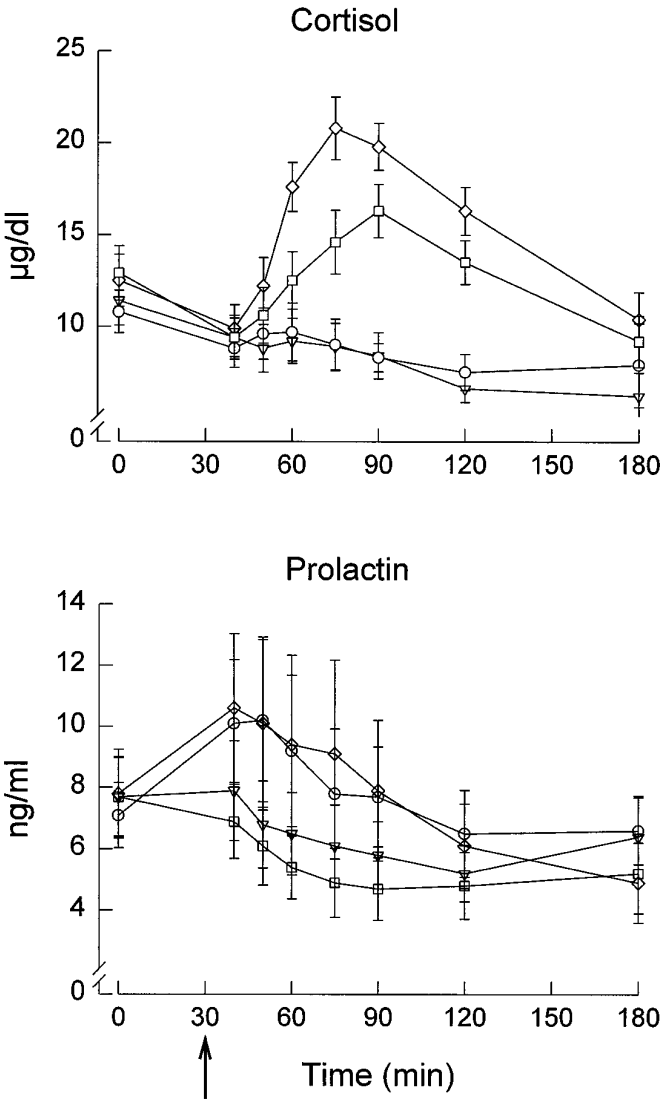

Fig. 5. Time course (mean ± S.E.M., $n = 8$) of cortisol and prolactin plasma concentrations. Other details of the figure are similar to those for figure 1.

yai *et al.*, 1992a; Sarnyai *et al.*, 1992b). Moreover, bilateral lesions of paraventricular nucleus decreased the ability of cocaine to induce the release of ACTH (Rivier and Lee, 1994). The elevations of ACTH are probably dose-dependent (Borowsky and Kuhn, 1991; Torres and Rivier, 1992). It may be that this mechanism is mediated through effects on different sites, including dopaminergic (Borowsky and Kuhn, 1991), serotonergic (Borowsky and Kuhn, 1991; Levy *et al.*, 1991) and N-methyl-D-aspartate (Torres *et al.*, 1994) receptors, as well as by the local anesthetic properties of cocaine (Calogero *et al.*, 1989). It is well known that cocaine binds specifically to uptake sites for dopamine, norepinephrine and serotonin. Acute administration of cocaine increases dopamine concentrations in synaptic clefts, mimicking the effects of dopamine and dopaminergic agonists (Gawin, 1991).

In cocaine-dependent subjects, the i.v. administration of 30 mg of cocaine produced an increase in ACTH plasma levels that was parallel to drug plasma concentrations and cocaine-induced cardiovascular and subjective effects (Mendelson *et al.*, 1992a; 1992b). The administration of the partial opioid agonist buprenorphine suppressed the acute cocaine-induced stimulation of both ACTH and euphoria (Mendelson *et al.*, 1992b). In i.v. cocaine abusers, the i.v. administration of 40 mg of cocaine produced an increase in cortisol plasma levels (Baumann *et al.*, 1995). It has been postulated that cocaine increases ACTH pulse amplitude *via* stimulation of CRF release from the hypothalamus (Teoh *et al.*, 1994). Some authors suggest that CRF could explain some of the behavioral actions of cocaine. In rats, cocaine-induced locomotor hyperactivity might be mediated, at least in part, through activation of the endogenous CRF system in the brain (Sarnyai *et al.*, 1992a). Mendelson and associates (1988) found that during cocaine withdrawal, cortisol levels were within normal limits. In pulse frequency analysis of cortisol, no differences were found between cocaine users and age-matched controls (Mendelson *et al.*, 1989). Accordingly, the increases in cortisol plasma levels found in our study may be attributable to the effects of cocaine on hypothalamic neurons releasing CRF, which, in turn, would stimulate the secretion of ACTH and cortisol.

Higher increases in cortisol plasma concentrations were found after the concurrent use of alcohol and cocaine than with cocaine alone. It is likely that this effect is related to the higher concentrations of cocaine and cocaethylene achieved with the drug combination. In experimental studies, cocaine-induced corticosterone increases are dose-dependent and are possibly related to cocaine plasma levels (Borowsky and Kuhn, 1991; Torres and Rivier, 1992). In humans, a concentration-effect relationship has been described for cardiovascular and subjective effects after the administration of i.v. cocaine, although the effects declined more rapidly than cocaine plasma concentrations. This result suggested the development of an acute tolerance phenomenon (Chow *et al.*, 1985; Ambre *et al.*, 1988; Foltin and Fischman, 1991). Although in our study, cortisol concentrations remained unchanged after the administration of alcohol, the presence of alcohol cannot be ruled out as a facilitating factor for the release of cortisol induced by cocaine.

Plasma concentrations of prolactin increased after the administration of alcohol, a pattern of response already observed by others after doses of alcohol between 0.75 and 1.3 g/kg (Schuckit *et al.*, 1983, 1987a; Ida *et al.*, 1992). The precise mechanism of this effect is poorly understood. An inhibition of dopamine secretion by the hypothalamus has been suggested (Ida *et al.*, 1992). After alcohol exposure, numerous changes in the rate of turnover and in brain tissue levels of different neurotransmitters and neuromodulators (dopamine, ACh, norepinephrine, TRH, arginine vasopressin) have been described (Emanuele *et al.*, 1992). Changes in dopamine, TRH or vasopressin levels may account for important variations in the plasma concentrations of prolactin. Increased basal prolactin levels and exaggerated responses to TRH have been described in alcoholics (Noth and Walter, 1984; Theoh *et al.*, 1992).

It has been shown that dopamine reuptake in dopaminergic neurons is inhibited by cocaine. This results in a prolonged dopamine concentration at the neuronal synapses and in stimulation of dopamine receptors. After chronic administration, cocaine may cause a depletion of neuronal dopamine. A synaptic decrease of dopamine has been related to withdrawal symptoms associated with cocaine dependence (Gawin, 1991). In fact, drugs with dopamine agonist proper-

TABLE 2

Pharmacokinetic parameters for alcohol, cocaine and its metabolites (values are mean ± S.D., $n = 8$)

Parameters	Alcohol Conditions		P
	Alcohol	Alc/Coc	
Alcohol			
C_{max} (μg/ml)	1196.4 ± 208.8	1003.4 ± 172.4	*
T_{max} (min)	54.1 ± 19.0	76.0 ± 27.7	N.S.
AUC_{0-390} (10^3 μg · min/ml)	243.6 ± 23.6	227.7 ± 23.7	N.S.
	Cocaine Conditions		P
	Cocaine	Alc/Coc	
Cocaine			
C_{max} (ng/ml)	273.7 ± 124.2	330.5 ± 111.7	*
T_{max} (min)	55.0 ± 28.1	41.3 ± 22.3	N.S.
AUC_{0-360} (10^3 ng · min/ml)	42.6 ± 16.7	51.1 ± 14.4	**
Benzoylecgonine			
C_{max} (ng/ml)	679.1 ± 186.8	484.8 ± 97.3	**
T_{max} (min)	138.8 ± 29.8	187.5 ± 74.6	N.S.
AUC_{0-1440} (10^3 ng · min/ml)[a]	476.8 ± 134.7	400.9 ± 105.2	*
Ecgoninemethylester			
C_{max} (ng/ml)	98.9 ± 16.6	96.3 ± 19.2	N.S.
T_{max} (min)	125.6 ± 38.2	144.4 ± 35.1	N.S.
AUC_{0-360} (10^3 ng · min/ml)	22.2 ± 4.1	21.5 ± 3.6	N.S.
Norcocaine			
C_{max} (ng/ml)	4.4 ± 4.2	6.4 ± 3.4	N.S.
T_{max} (min)	114.0 ± 33.7	85.7 ± 31.8	N.S.
AUC_{0-360} (ng · min/ml)	702.8 ± 652.3	979.7 ± 712.1	*
Cocaethylene			
C_{max} (ng/ml)		48.4 ± 14.7	
T_{max} (min)		116.3 ± 9.9	
AUC_{0-360} (10^3 ng · min/ml)		10.1 ± 3.5	
Norcocaethylene			
C_{max} (ng/ml)		3.3 ± 1.6	
T_{max} (min)		124.3 ± 44.4	
AUC_{0-360} (ng · min/ml)		604.7 ± 476.2	

Alc/Coc = alcohol-cocaine combination. Student's t test for paired data statistical significance: * $P < .05$; ** $P < .01$.
[a] AUC for benzoylecgonine was calculated from 0 to 1440 min.

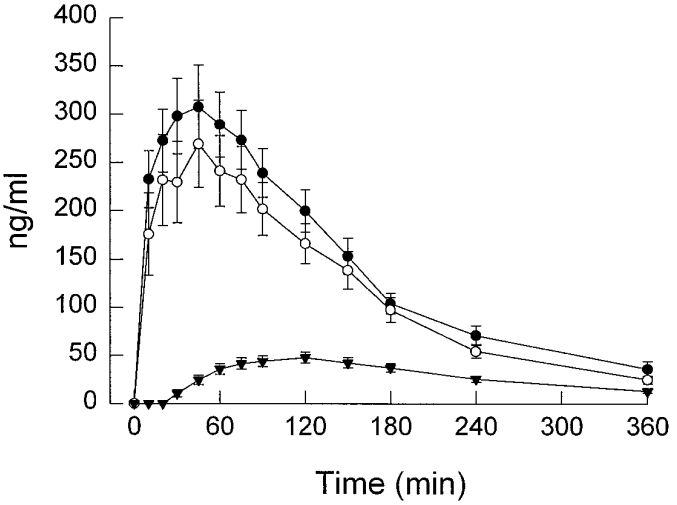

Fig. 6. Time course (mean ± S.E.M., $n = 8$) of cocaine and cocaethylene plasma concentrations. Symbols are used as follows: ○, cocaine concentrations after cocaine administration; ●, cocaine concentrations after cocaine and alcohol administration; ▼, cocaethylene concentrations after cocaine and alcohol administration.

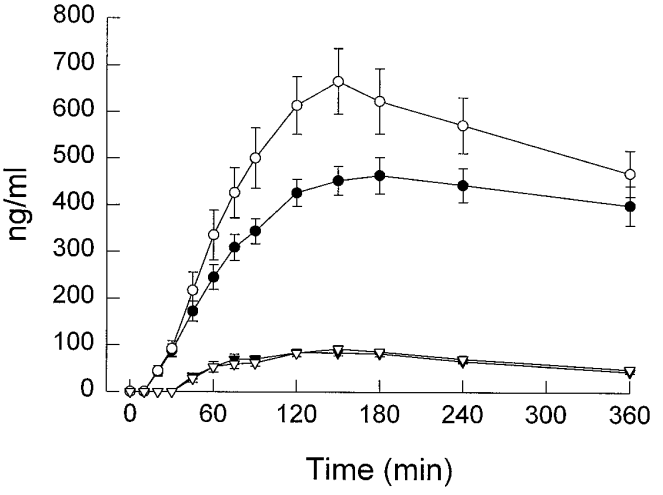

Fig. 7. Time course (mean ± S.E.M., $n = 8$) of benzoylecgonine and ecgoninemethylester plasma concentrations. Symbols are used as follows: ○, benzoylecgonine concentrations after cocaine administration; ●, benzoylecgonine concentrations after cocaine and alcohol administration; ▽, ecgoninemethylester concentrations after cocaine administration; ▼, ecgoninemethylester concentrations after cocaine and alcohol administration.

ties have successfully been used in the management of cocaine dependence (Gawin, 1991). Dopamine is the regulating factor of prolactin secretion by means of D_2 receptors. Substances that produce neuronal dopamine increases (e.g., dopamine agonists) inhibit prolactin release; by contrast, neuronal dopamine decreases are associated with hyperprolactinemia. Vasoactive intestinal peptides and TRH, both secreted by pituitary cells, are other important stimulants of prolactin secretion.

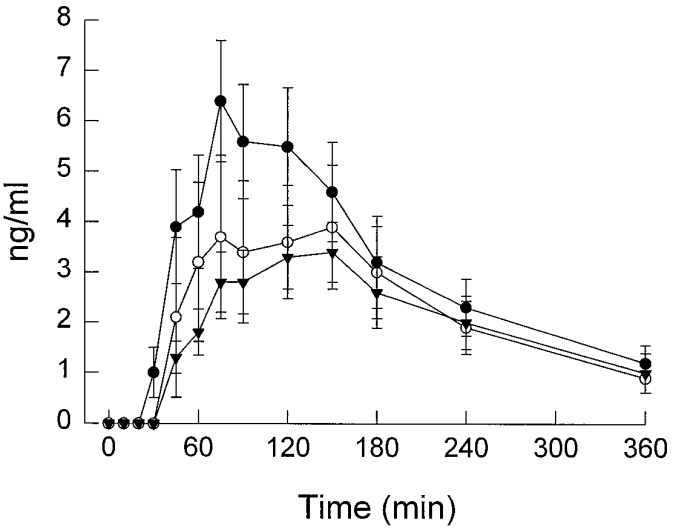

Fig. 8. Time course (mean ± S.E.M., $n = 8$) of norcocaine and norcocaethylene plasma concentrations. Symbols are used as follows: ○, norcocaine concentrations after cocaine administration; ●, norcocaine concentrations after cocaine and alcohol administration; ▼, norcocaethylene concentrations after cocaine and alcohol administration.

The acute administration of cocaine induces a decrease in prolactin concentrations both in experimental animals and in humans. In rhesus monkeys, either female in follicular phase or male, i.v. cocaine decreased prolactin levels (Mello *et al.*, 1990a, 1990b; Mello *et al.*, 1993). A rebound increase in prolactin concentration appeared 90 to 110 min after the administration of cocaine (Mello *et al.*, 1990b). Chronic self-administration of cocaine in rhesus monkeys produced basal prolactin levels in the low normal range. The pattern of dopamine-induced supression of prolactin was similar to that described after acute administration in non–cocaine-dependent animals. However, postdopamine hyperprolactinemia showed an increase (Mello *et al.*, 1994). In ovariectomized female rhesus monkeys, the administration of i.v. cocaine failed to decrease prolactin levels, a result that reflects the important role of gonadal steroids in anterior pituitary hormone secretion (Mello *et al.*, 1995).

In this study, plasma prolactin concentrations were slightly lower as compared with placebo, although statistically significant differences were not found. Recently, Heesch *et al.* (1996), reported a significant decrease in prolactin concentrations in 12 healthy subjects after the intranasal administration of cocaine (2 mg/kg). The differences with placebo were observed at 60 to 120 min after cocaine administration. Several possibilities may be suggested to explain the discrepancy between their results and ours, such as dose of cocaine (100 mg *vs.* at least 140 mg [the volunteers' weight is not provided in their paper]), the number of subjects (8 *vs.* 12), which could decrease the variability and increase the statistical power, and the number of statistical comparisons (multiple in our investigation [four conditions, six comparisons using the conservative Tukey test], and a single comparison in their experiment). In cocaine-dependent subjects, the acute administration of cocaine (30 mg i.v.) was followed by a decrease in prolactin for 120 min as compared with base line (Mendelson *et al.*, 1992a), although differences as compared with placebo were not statistically significant. Similar results were reported by Baumann *et al.* (1995) when 40 mg of cocaine was administered to i.v. cocaine abusers. Decreased, increased, and normal plasma prolactin concentrations have been reported after discontinuation of cocaine use (Gawin and Kleber, 1985; Mendelson *et al.*, 1988; Swartz *et al.*, 1990). Hyperprolactinemia seems to be a prognostic factor for relapse after cocaine withdrawal (Teoh *et al.*, 1990; Weiss *et al.*, 1994).

The effects of the alcohol and cocaine combination on prolactin regulation in humans have not been previously described. We found that alcohol-induced hyperprolactinemia was not altered by the drug combination. Although cocaine produced a slight decrease in plasma concentrations of prolactin when administered alone, it could not antagonize the effects of alcohol on prolactin secretion when alcohol and cocaine were given simultaneously.

The results of alcohol pharmacokinetics are in agreement with a previous study of our group (Farré *et al.*, 1993). C_{max} was slightly lower in the combination condition, and there were no differences in T_{max} or AUC values. Other authors reported similar findings when both drug were administered simultaneously (McCance-Katz *et al.*, 1993). The order of drug administration seems to be an important factor. The difference in peak blood levels of alcohol disappeared when the alcohol beverage was drunk 30 min after cocaine snorting (Perez-Reyes, 1994). Blood alcohol levels were marginally lower during the first hour in the kinetics of the drug combination condition. This differences could be related to changes in the alcohol absorption rate. The amount of alcohol diverted to cocaethylene synthesis does not seem to account for the differences in plasma levels of alcohol.

Cocaine and norcocaine blood levels were higher in the combination condition, as shown by the AUC values. Benzoylecgonine concentrations were lower after drug combination, with differences in C_{max} and AUC values. No differences were found in ecgoninemethylester pharmacokinetic parameters. Cocaethylene and norcocaethylene appeared only in the combination condition. The concentrations of cocaethylene increased slowly, with a maximal peak 2 hr after cocaine administration. As mentioned previously, cocaethylene is an active metabolite that produces euphoria and cardiovascular effects slightly less than or similar to those of cocaine (Perez-Reyes *et al.*, 1994; McCance *et al.*, 1995). Taking into account the ratio between cocaethylene and cocaine concentrations over the study period, we find that cocaethylene accounted for 8%, 12%, 18%, 24%, 36% and 39% of cocaine concentration at 45, 60, 90, 120, 180 and 240 minutes after drug administration. Because of the high sensitivity of the analytical methodology, it was possible to detect norcocaethylene in plasma after the consumption of cocaine doses compatible with the recreational use of alcohol and intranasal cocaine. This is the first description of norcocaethylene pharmacokinetics in humans. Other pharmacokinetic findings were consistent with previous reports (Perez-Reyes and Jeffcoat, 1992; Farré *et al.*, 1993; McCance-Katz *et al.*, 1993).

In terms of relative bioavailability, although the AUC for cocaine was greater in the combination condition, the AUC for benzoylecgonine (a major metabolite of cocaine) was higher in the cocaine condition. The sum of the AUCs of cocaine and its metabolites (benzoylecgonine, ecgoninemethylester, cocaethylene, norcocaine and norcocaethylene), as an index of absorption of the drug, was not different when cocaine alone (617,563 ng · min/ml [2183.8 nmol · min/ml]) and

cocaine-alcohol conditions were compared (572,864 ng · min/ml [2019.4 nmol · min/ml]). These results of relative bioavailability agree with a previous study (Farré *et al.*, 1993). Cocaine is metabolized to benzoylecgonine by spontaneous hydrolysis in plasma and especially by the action of an hepatic nonspecific cocaine carboxylesterase (Inaba *et al.*, 1978; Inaba, 1989; Dean *et al.*, 1991). In the presence of ethanol, this enzyme is responsible for the transesterification of cocaine, which forms the active metabolite cocaethylene (Brzezinski *et al.*, 1994). Because the same enzyme regulates both metabolic pathways, an inhibition of metabolism (possibly a competitive inhibition) may explain our findings of increased cocaine concentrations, decreased benzoylecgonine levels and the appearance of cocaethylene when cocaine and alcohol were given simultaneously. This assumption may be supported by the observation of a decreased clearance of cocaine in the drug combination condition found in a previous study (Farré *et al.*, 1993). As we have said, the order of drug administration could be a crucial factor in this interaction. Perez-Reyes and colleagues (1994) did not find differences in cocaine concentrations when alcohol was administered 30 min after cocaine snorting.

The higher plasma concentrations of cocaine in the drug combination condition could favor an increased availability of the substrate for the N-demethylation of cocaine, resulting in higher levels of norcocaine (Farré *et al.*, 1993).

The time course of blood levels of norcocaethylene in experimental conditions in humans has not been described before. Cocaethylene is N-demethyled to norcocaethylene. The rate of metabolic biotransformation by oxidative N-demethylation seems greater for cocaethylene to norcocaethylene than for cocaine to norcocaine. Judging by the relation of AUCs between the substrates (cocaethylene or cocaine) and metabolites (norcocaethylene or norcocaine) as a possible index of oxidative metabolic rate, the N-demethylation of cocaethylene to norcocaethylene is 3-fold greater than that of cocaine to norcocaine.

When the overall effects of both conditions that include cocaine are considered, it seems that there is a relationship between cocaine levels and cardiovascular and subjective effects as well as plasma cortisol levels. Some of the effects reached their maximum around the peak of cocaine concentration, with similarities in effect-time and concentration-time curves. Statistically significant increases in HR, blood pressure, subjective euphoria-related effects and plasma cortisol found in the combination condition as compared with cocaine alone may be explained by pharmacodynamic and/or pharmacokinetic alcohol-cocaine interactions (e.g., a decrease in cocaine transformation to benzoylecgonine that may be due in part to a competitive inhibition of metabolism to form cocaethylene). The interaction resulted in a significant increase in plasma cocaine concentrations (20% higher in the combination condition), and the presence of cocaethylene, an active metabolite, that represented 20% of the cocaine concentrations. In our opinion, initially increased plasma cocaine levels, followed by the additive effect of cocaethylene, might explain the enhancement of cocaine effects in the combination condition.

In summary, the administration of alcohol and cocaine increased the cardiovascular, subjective and cortisol response to cocaine and decreased some of the subjective effects of alcohol intoxication. The administration of cocaine did not alter the effects of alcohol on prolactin secretion.

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