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Alcohol and Cocaine Interactions in Humans[1]

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ABSTRACT

The effects of 100 mg of intranasal cocaine (COC) in acute alcohol intoxication (1 g/kg) was assessed in nine experienced and non-dependent healthy volunteers in a double-blind, controlled, randomized, cross-over clinical trial. Alcohol alone impaired psychomotor performance, whereas COC alone produced subjective effects related to euphoria and well-being, improved the reaction time and increased heart rate and blood pressure. The combination of COC and alcohol induced a nonsignificant decrease in the subjective feelings of drunkenness, an increase in COC-induced euphoria, a significant improvement in alcohol-related changes in psychomotor performance and a marked increase in heart rate. Subjects experienced subjective and performance effects that could be self-interpreted as more pleasant compared to the effects of alcohol alone. When alcohol was given simultaneously, COC plasma levels were higher (possibly as a result of an inhibition of hepatic metabolism of COC produced by alcohol), norcocaine plasma levels almost doubled and cocaethylene was detected in plasma, so that its basic pharmacokinetic profile could be described. The simultaneous use of both drugs produced changes in heart rate and blood pressure that could increase the risk of cardiovascular toxicity associated with the use of COC.

The combined cocaine-ethanol abuse is a very prevalent problem in Europe and the United States (Grant and Hartford, 1990; Camí and Barrio, 1993). In forensic studies, both drugs are frequently identified in biological samples from fatally injured drivers (Budd *et al.*, 1989; Marzuk *et al.*, 1990). The pharmacologic effects of the combination of COC and alcohol have been studied in different animal species and behavioral models with controversial results. Two studies using laboratory rats reported an increase in the sedative effect of alcohol (Rech *et al.*, 1976; Misra *et al.*, 1989), whereas in two other experiments, ethanol potentiated the stimulant actions of COC (Aston-Jones *et al.*, 1984; Masur *et al.*, 1989).

A metabolite of COC, CE-ethyl ester of benzoylecgonine or ethylcocaine, has been reported in individuals using COC and ethanol concurrently (Rafla and Epstein, 1979; Jatlow *et al.*, 1991). It has been shown that CE potently inhibits presynaptic dopamine uptake *in vitro* (Hearn *et al.*, 1991) and effectively substitutes for COC in a drug discrimination protocol in rats (Woodward *et al.*, 1991). In healthy volunteers, the combination of ethanol and COC produced greater increases in heart rate and blood pressure than that observed after COC alone (Foltin and Fischman, 1989). However, no published data exist on the effects of the combination of alcohol and COC on subjective, performance measures or on the precise mechanisms involved in the pharmacologic interactions of these two drugs. This information may be relevant when determining toxicologic consequences of the simultaneous use of COC and alcohol.

The present study was designed to assess the effects of COC in acute alcohol intoxication by evaluating subjective effects, changes in heart rate and blood pressure, psychomotor performance tasks and the pharmacokinetics and metabolic profile of these drugs.

Methods

Subjects. Subjects were recruited by "word of mouth" and notices posted on the bulletin boards at the University. Eligibility criteria required the recreational use of COC by the intranasal route (on at least six occasions during the 3 months before participation in the study), a daily alcohol consumption of between 30 and 60 g and previous experiences in acute alcohol intoxication.

Nine healthy male volunteers were selected and paid for their participation in the study. The mean age and body weight were 27 years (range 22–30) and 66.6 kg (range 55.5–79.7), respectively. Their average consumption of alcohol was 40 g/day and of COC use by the intranasal route, twice per month in the previous year. All but two subjects were smokers. None had a history of drug dependence or i.v. drug use. Subjects were informed they would receive COC, alcohol or placebo in different combinations. Each subject passed a physical examination and a laboratory screening. A signed informed consent was also pro-

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ABBREVIATIONS: COC, cocaine; CE, cocaethylene; TERT-BUOH, *tert*-butyl alcohol; ETOH, ethanol; BE, benzoylecgonine; EME, ecgoninemethylester; NC, norcocaine; AUC, area under the curve; ANOVA, analysis of variance.

vided by all participants. The study was approved by the Ethical Committee of our institution and was authorized by the Ministry of Health ("Dirección General de Farmacia y Productos Sanitarios" 87/334).

Study design. Subjects participated as outpatients in seven sessions in which the same doses and preparations of COC and alcohol were used. In each session they drank a beverage containing alcohol or its placebo, and snorted a powder containing COC or its placebo. After a washout period of 72 hr, each subject was taken to a quiet room at the same time each morning. Sessions lasted 8 hr, throughout which time subjects remained seated except for visits to the bathroom. Two hours after the start of each session subjects had a light breakfast. Tobacco smoking was not permitted during the first 2 hr of the session.

Three training sessions were carried out to familiarize the volunteers with testing procedures and to assess their tolerance to the drugs. During the first session they received both placebos and in the following two sessions, COC or alcohol were given at random. Results from the training sessions are not included.

Four study sessions were carried out during which different combinations of drugs were given in a double-blind fashion. Combinations were as follows: placebo snorted/alcohol oral (alcohol condition), COC snorted/placebo oral (COC condition), COC snorted/alcohol oral (drug combination condition) and placebo snorted/placebo oral (placebo). The sequences of treatment were randomized using a 4 × 4 latin square cross-over design.

Drugs. COC HCl (pharmaceutical grade) was provided by the Ministry of Health. COC 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 COC preparation was used as placebo given that it has been reported that at these doses, blood COC 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 30 × 15 cm steel plate and prepared their own two "lines" using a straight-edge razor. When instructed they inhaled the powder using a straw, one line for each nostril.

Acute alcohol intoxication was induced by the ingestion of vodka and tonic water containing a total alcohol dose of 1 g/kg. Several drops of aromatic bitters and lemon juice were added to mask successfully the placebo drink which contained tonic water only (Camí *et al.*, 1988). The total volume of liquid was 450 ml. The subjects were given 30 min to consume the beverage, drinking 150 ml every 10 min. When the drink was finished, the subjects snorted the powder. After this sequence of administration the peak effect of both drugs on subjective and psychomotor tasks was obtained at about the same time.

Heart rate and blood pressure. Heart rate and blood pressure were recorded at −30, 0 (immediately before beverage administration), 14, 28 (before powder snorting), 35, 42, 48, 53, 59, 67, 72, 82, 90, 120, 180, 240, 300, 360, 510 and 1440 min using a Sentry Automatic Monitor (Automated Screening Devices, Costa Mesa, CA). For safety reasons, ECG and pulse were continuously monitored during the first 4 hr of the session (Hewlett-Packard model 78353B, Palo Alto, CA).

Subjective effects. Subjective effects were measured using a set of 14 different visual analog scales (100 mm) marked at opposite ends with "not at all" and "extremely." Subjects described effects in the following terms: "high," "drunk," "any effect," "good effects," "bad effects," "liking," "feeling good," "energetic," "better performance," "worse performance," "clear-headed," "content," "anxious" and "drowsy." The visual analog scales were administered at 0 (before beverage administration), 14, 28, 30 (immediately after powder snorting), 35, 38, 42, 48, 51, 59, 67, 75, 82, 90, 105, 120, 180, 240 and 510 min.

Psychomotor performance. The psychomotor performance battery included four different tests which were selected on the basis of their known sensitivity to the effects of alcohol (Mitchell, 1985; Hindmarch *et al.*, 1991).

The simple reaction time, a measure of the sensory-motor performance (Hindmarch, 1980), was assessed using the Vienna Reaction Unit (PC Vienna System, Schufried, Austria) comprising one colored response button adjacent to a yellow light-emitting diode. Using whichever finger they preferred upon illumination of the light, subjects were asked to remove their finger from a "control" button, and depress the button adjacent to the light, as quick as possible and then return the finger to depress the control button until the light was once more illuminated. The simple reaction time is the sum of two components: the decision time (time taken to release the control button) and the motor time (time taken to move the finger and depress the response button adjacent to the illuminated light). The length of the intervals during which light stimulus was presented varied during the 50 tests carried out. Results in milliseconds are expressed as the mean of the response time to the 50 stimuli.

The critical flicker fusion frequency, an indicator of central nervous system integration and cortical arousal and fatigability (Hindmarch, 1980; Curran, 1990) was measured in increasing and decreasing modes during three consecutive cycles (Flicker Fusion Analyzer-PC Vienna System). During the increasing mode, subjects were required to depress a response button when a flickering light gave rise to the subjective sensation of a steady light (from flicker to fusion). In the decreasing mode, the response was required to be made when a steady light became a flickering one (from fusion to flicker). Results were expressed in hertz and presented as the mean of the three cycles for each mode.

The Maddox-Wing device (Clement Clark, London, United Kingdom) was used to measure heterophoria (exophoria). This test provides an index of the relaxation of the extraocular musculature. It is sensitive to the effects on the central nervous system of different sedative drugs (Hannington-Kiff, 1970; Manner *et al.*, 1987).

The Pauli test, an indicator of central nervous system processing capacities and concentration ability (Hindmarch, 1980; Patat *et al.*, 1988), is an arithmetical task that requires the calculation of the sum of two numbers. It is included in the work performance test series (PC Vienna System). The numbers appeared in the top and the bottom part of a video screen and the subject entered the correct response by pressing a key on a numeric keypad. If the answer was a two-digit number, the correct answer for this task was the last digit (*i.e.*, 5 + 7 = 12, enter "2"). Subjects were instructed to complete as many sums as possible. Results were expressed as the number of sums correctly completed during a 4-min test.

In each session, the simple reaction time test was administered first followed by the critical flicker fusion frequency, the Maddox-Wing and the Pauli tests. The completion of the test battery took around 15 min. The subjects completed the battery three times at −30 (before drug administration), 45 and 90 min after beverage administration (or 15 and 60 min after powder snorting). Before taking the tests, subjects underwent training sessions. They completed the simple reaction time task on 20 occasions and the critical flicker fusion frequency on five. The criteria for a stable response in the training for the Pauli test was a coefficient of variation less than 5% in the number of correct responses in five consecutive trials when at least 20 had been performed.

Blood sampling. An indwelling intravenous catheter was inserted into a subcutaneous vein in the forearm of the non-dominant arm and normal saline solution was infused at a rate of 20 ml/hr. Blood samples (2 ml) were obtained for analysis of alcohol at 0, 14, 28, 42, 59, 72, 87, 120, 180, 240, 300, 360, 510 and 1440 min after beverage administration. The whole blood was collected in a plastic 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-BUOH.

Blood samples (8 ml) for the analysis of COC and its metabolites were also obtained at 0, 35, 42, 51, 59, 72, 87, 105, 120, 150, 180, 240, 300, 360, 510 and 1440 min after beverage administration (or −30, 5, 7, 21, 29, 42, 57, 75, 90, 120, 150, 210, 270, 330, 480 and 1410 min after powder snorting). Blood samples for the analysis of unchanged COC 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.

Drug analysis. Blood alcohol levels were measured by gas-liquid

chromatography using a head-space injection technique and flame ionization detection (Hewlett-Packard 19395A), which permitted measurement of ETOH down to levels of 60 μg/ml (four times the signal-to-noise ratio). Separation was carried out using a cross-linked capillary column (ref. RSL-160) 5 m long × 0.530 mm external diameter (0.33 μm film thickness).

Standard curves for calibration were prepared with blank human blood over the concentration range of 79 to 1580 μg/ml for ETOH. Peak-height ratios between ETOH and the internal standard (TERT-BUOH) were subjected to least square regression analysis. Good linearity of the height ratio (x) of the internal standard *vs.* concentration (y) was obtained over the ranges studied (r = 0.999, y intercept = 16, slope = 835) for ETOH. Between-day coefficients of variation of control blood samples (n = 5) were 7.57, 1.21 and 0.97% for 79, 197.5 and 1580 μg/ml of ETOH levels, respectively.

Blood levels of COC and the metabolites BE, EME, NC and CE were determined by gas chromatography coupled with mass spectrometry. A gas chromatograph (Hewlett-Packard model 5890A) fitted with an autosampler (model 7673A) was coupled to a mass selective detector (model 5970). Separation was carried out using a cross-linked capillary column (Hewlett-Packard) 25 m long × 0.2 mm external diameter, 5% phenylmethyl silicone gum (0.33 μm film thickness). The mass spectrometer was operated by electron impact ionization (70 eV) and in the single-ion monitoring acquisition mode. From electron impact ionization mass spectra the following ions were selected for monitoring the analytes grouped into five successive different acquisition groups: group 1 m/z 182 for EME; group 2 m/z 318 for BE; group 3 m/z 182 for COC; group 4 m/z 196 and 313 for CE and NC, respectively and group 5 m/z 331 for the internal standard, propylcocaine.

Bond Elut Certify (Varian, Harbor City, CA) columns were inserted into a vacuum manifold and conditioned by washing once with 2 ml of 0.1 M phosphate buffer at pH 7. The columns were prevented from running dry before applying the sample. Aliquots of 1 ml of plasma were centrifuged at 3,000 g × 10 min and transferred to clean polystyrene tubes to which 25 μl (250 ng) of a methanolic solution of propylcocaine and 1.5 ml of 0.1 M phosphate buffer (pH 7) were added. Samples were poured into each column and gently sucked through. The columns were successively washed with 3 ml of deionized water, 3 ml of 0.1 M hydrochloric acid and 9 ml of methanol. Elution of the analytes was performed with 2 ml of a mixture of chloroform [isopropyl alcohol, 80:20 (v/v)] containing 2% ammonium hydroxide. The eluates were collected and evaporated to dryness under a gentle nitrogen stream at room temperature, and kept in a desiccator under vacuum for 2 hr before derivatization of the residues. Pentafluoropropionic anhydride (80 μl) and 1,1,1,3,3,3-hexafluor-2-propanol (20 μl) were added to the dried residue and vortexed for 10 sec. The tubes were incubated at 60°C for 15 min. After drying, the residues were redissolved in 50 μl of ethyl acetate and 2 μl of the solution was injected into the chromatographic system.

Standard curves for calibration were prepared with blank human plasma over the concentration range of 50 to 500 ng/ml for COC and EME, 50 to 1000 ng/ml for BE, 10 to 200 ng/ml for CE and 1 to 15 ng/ml for NC. The recoveries (mean ± S.D.; n = 4) were 98 ± 2% for COC, 87 ± 5% for BE, 97 ± 3% for EME, 93 ± 7% for CE and 98 ± 2% for NC over their corresponding range of concentrations. Peak-height ratios (x) between the analytes and the internal standard *vs.* the concentration (y) were subjected to least squares regression analysis. Good linearity (area ratio of the internal standard *vs.* concentration) was obtained over the ranges studied (r = 0.999, y intercept = 0.104, slope = 0.011 for COC; r = 0.997, y intercept = 1.005, slope = 0.036 for BE; r = 0.997, y intercept = 0.720, slope = 0.030 for EME; r = 0.999, y intercept = 0.03, slope = 0.010 for CE; r = 0.999, y intercept = −0.001, slope = 0.023 for NC). The sensitivity (4 times the signal-to-noise ratio) achieved for COC, BE, EME, CE was 1 ng/ml and 0.5 ng/ml for NC. Between-day coefficients of variation of control blood samples (n = 13, 70 ng/ml for COC, BE, EME; 20 ng/ml for EC and 2 ng/ml for NC) ranged between 8.9% for COC to 17.7% for NC.

Data analysis. Data from all four drug conditions were analyzed by repeated measures two-way ANOVA with drug condition and time as factors. A second set of analyses was conducted using repeated measures one-way ANOVA for peak drug effects (or peak changes from baseline) with drug condition as the factor. Tukey's post-hoc tests were then used to compare all possible pairs of conditions. Pharmacokinetic parameters evaluated were peak concentration (C_{max}), the time taken

TABLE 1

Statistical results of physiological, subjective and psychomotor performance evaluations (peak effects)

Abbreviations used are: P, placebo cocaine/placebo alcohol; A, placebo cocaine/alcohol; C, cocaine/placebo alcohol; C/A, cocaine/alcohol; CFF, critical flicker fusion. Tukey post-hoc condition comparisons: * P < .05. N.S., not significant. If blank, not done (ANOVA not significant).

Variable	F (3,24)	P Value	P			C		A
			C/A	C	A	C/A	A	C/A
Heart rate	17.07	<0.0001	*	*	N.S.	*	N.S.	*
Systolic pressure	9.35	0.0003	*	*	N.S.	N.S.	*	*
Diastolic pressure	3.74	0.0245	*	N.S.	N.S.	N.S.	N.S.	*
High	9.40	0.0003	*	*	N.S.	N.S.	*	*
Drunk	18.96	<0.0001	*	N.S.	*	*	*	N.S.
Any effect	9.25	0.0003	*	*	*	*	N.S.	N.S.
Good effects	9.00	0.0004	*	*	N.S.	*	N.S.	*
Bad effects	4.18	0.0162	N.S.	N.S.	*	N.S.	*	N.S.
Liking	6.38	0.0025	*	*	N.S.	N.S.	N.S.	*
Feeling good	8.13	0.0007	*	N.S.	*	*	N.S.	*
Energetic	5.33	0.0059	*	N.S.	N.S.	N.S.	N.S.	N.S.
Better performance	4.47	0.0125	*	N.S.	N.S.	N.S.	N.S.	N.S.
Worse performance	5.83	0.0039	*	N.S.	*	N.S.	*	N.S.
Clear-headed	5.83	0.0039	*	N.S.	N.S.	N.S.	N.S.	*
Content	7.64	0.0009	*	N.S.	*	N.S.	*	N.S.
Anxious	2.17	0.1183						
Drowsy	8.23	0.0006	N.S.	N.S.	*	N.S.	*	*
Simple reaction time	17.90	<0.0001	N.S.	N.S.	*	N.S.	*	*
Decision time	11.99	0.0001	N.S.	*	*	N.S.	*	*
Motor time	29.13	<0.0001	*	N.S.	*	*	*	*
CFF increasing	2.74	0.0658						
CFF decreasing	1.29	0.3019						
Pauli (correct)	16.17	<0.0001	*	N.S.	*	*	*	N.S.
Maddox-Wing	20.73	<0.0001	*	N.S.	*	*	*	N.S.

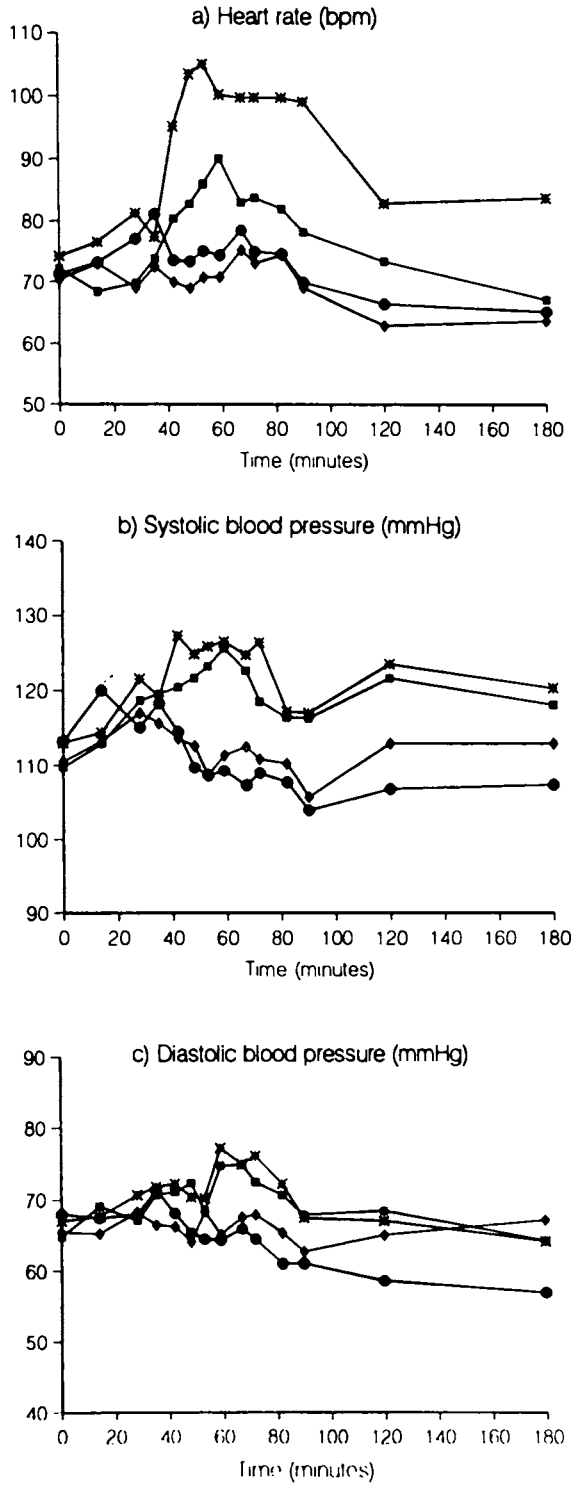

Fig. 1. Effects (mean, $n = 9$) of the four conditions studied on heart rate (a), systolic (b) and diastolic blood pressure (c). Symbols: *, cocaine-alcohol condition; ■, cocaine condition; ●, alcohol condition; ◆, placebo condition.

to reach the maximum concentration (T_{max}), and AUC from 0 to 360 (AUC_{0-360}) or 480 min (AUC_{0-480}) which was calculated by the trapezoidal rule. The AUC from 0 to infinite (AUC_{total}) was estimated by $AUC_{total} = AUC_{0-480} + C_p/kel$, where C_p was the last experimental plasma level and "kel" the first order elimination constant. Plasma clearance (Cl_p) and kel were estimated using an stripping computing program (Schumaker, 1986). The bioavailability of COC was estimated by comparison of the AUC calculated for the COC condition to other AUC described in the literature from i.v. pharmacokinetic studies of COC (Javaid *et al.*, 1983). The bioavailability was used to estimate the apparent volume of distribution (V_d) and its plasma clearance (Cl_p) in the presence and absence of ethanol.

Pharmacokinetic parameters were analyzed using a paired Student's t test and the Spearman correlation test. Results were considered statistically significant at $P < .05$.

Results

Heart rate. Alcohol had no effects on heart rate. COC produced an increase in heart rate in comparison with placebo. The drug combination produced an increased heart rate in comparison with placebo and COC, which was greater than that produced by COC alone and had a duration of more than 3 hr. The peak difference between the conditions of COC and placebo was 12 bpm, between placebo and the drug combination 33 bpm and between COC and the drug combination 21 bpm.

Blood pressure. Alcohol did not produce effects on blood pressure. COC caused an increase in systolic blood pressure as compared with placebo. The drug combination produced increases in systolic and diastolic blood pressure in comparison with placebo or alcohol. The peak difference in systolic blood pressure between COC and placebo conditions was 15 mm Hg, and between placebo and the drug combination conditions was 16 mm Hg. The peak difference in diastolic pressure in comparison with placebo was 12 mm Hg for the drug combination and 10 mm Hg for COC.

Cardiovascular effects after the administration of alcohol, COC, placebo or the drug combination are shown in table 1 and figure 1.

Subjective effects. Increases in the ratings of drunk, any effect, bad effects, feeling good, worse performance, content and drowsy scales were found when alcohol was given as compared with placebo. COC produced increases in the ratings of high, any effect, good effects and liking and the drug combination in those of high, drunk, any effect, good effects, liking, feeling good, energetic, better performance, worse performance, clear-headed and content as compared with placebo (table 1, fig. 2).

Ratings for the COC and the drug combination conditions were statistically different in the scales of drunk, any effect, good effects and feeling good with higher scores in the drug combination condition. The combination condition differed from the alcohol condition in the scales of high, good effects, liking, feeling good, energetic and clear-headed.

Psychomotor performance. In the simple reaction time, alcohol produced an increase in the total time, decision time and motor time in comparison with placebo (table 1, fig. 3). COC significantly improved the decision component of simple reaction time in comparison with placebo. This improvement was more marked at 90 min. The drug combination attenuated the deleterious effect of alcohol in the simple reaction time (total, decision and motor). This effect was particularly evident at 45 min. Although with the drug combination the subjects had a faster response in comparison with alcohol, their response speed was less than under the placebo or COC conditions.

In the analysis of the increasing and decreasing modes of the critical flicker fusion frequency, no differences were found between drug conditions (table 1).

In the Maddox-Wing device, the conditions of alcohol and the drug combination increased the degree of exophoria in comparison with those of placebo and COC. COC produced no

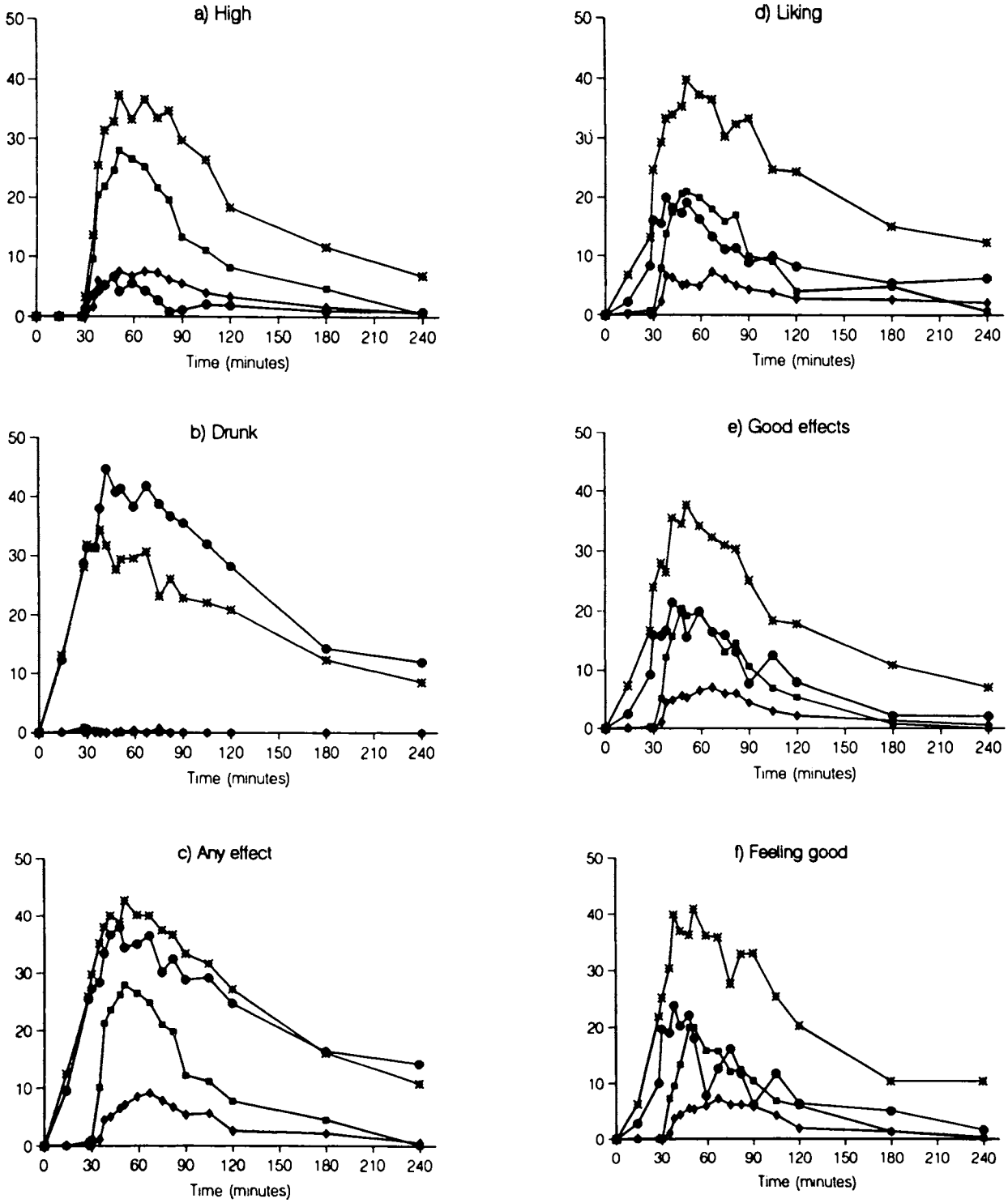

Fig. 2. Effects (mean, $n = 9$) of the four conditions studied on selected visual analog scales used for subjective effects evaluation: (a) high, (b) drunk, (c) any effect, (d) liking, (e) good effects, (f) feeling good. Symbols as in figure 1.

changes in exophoria, with diopter values similar to those obtained with placebo. No differences were found between the drug combination and alcohol conditions.

In the Pauli test, alcohol impaired performance producing a reduction in the number of correct responses (table 1, fig. 3). COC had no effect on this task, the total number of responses being similar to those obtained with placebo. Although the drug combination counteracted in part the effects of alcohol in this task, this effect did not reach statistical significance. However, performance under the drug combination was worse than under placebo or COC alone.

Pharmacokinetic data. When the two conditions containing alcohol were compared (table 2, fig. 4), no significant differences were found in the pharmacokinetic parameters except for C_{max}. During the first hour of the kinetic study, blood ETOH levels were slightly higher in the alcohol condition when compared with the condition receiving the drug combination.

Plasma levels of COC in the drug combination condition

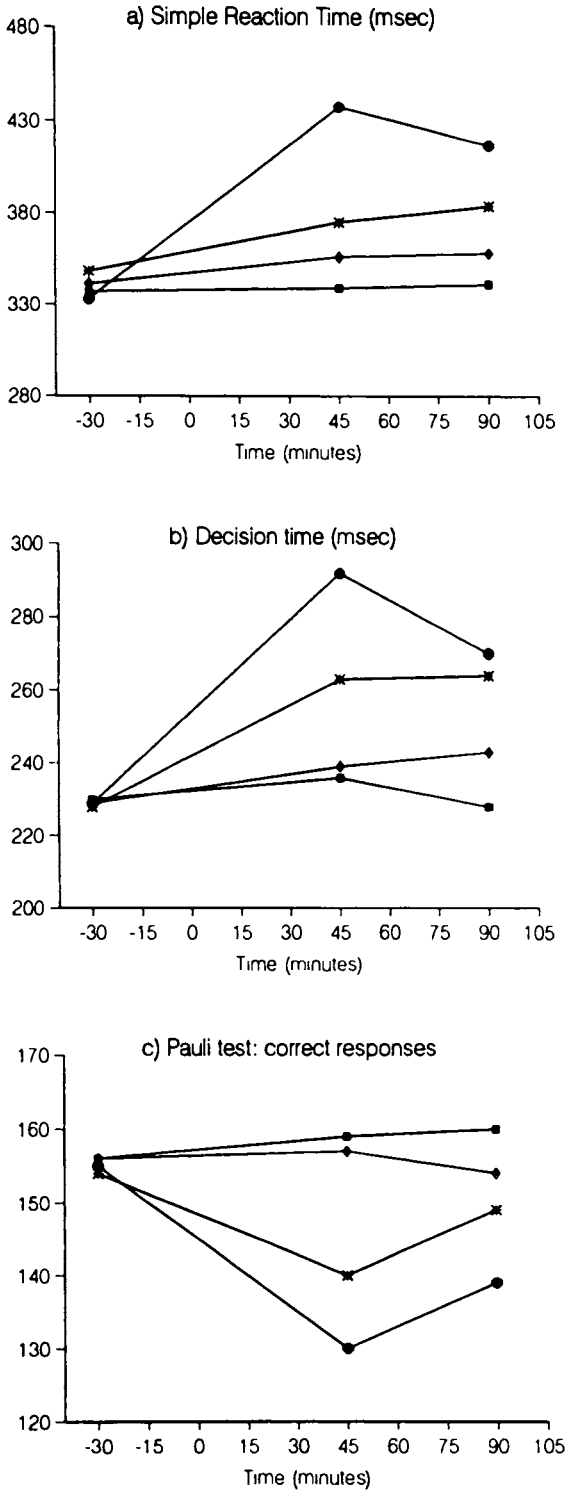

Fig. 3. Effects (mean, $n = 9$) of the four conditions studied on selected measures of psychomotor performance: (a) simple reaction time, (b) decision time, (c) pauli test. Symbols as in figure 1.

were higher than in the COC condition as reflected on AUC_{0-480}, AUC_{total} and C_{max} values (table 3, fig. 5). This finding was observed in each of the nine subjects. The bioavailability of cocaine was 0.8. There was a significant reduction in both Cl_p and V_d in the condition receiving the drug combination when compared with the COC condition (Cl_p, 1,424 *vs.* 2196 ng/ml/min, $P < .04$; V_d 153.1 ± 45.2 *vs.* 238 ± 81.9 liters, $P < .03$). A significant difference of approximately 20 min in T_{max} was

TABLE 2

Pharmacokinetic parameters for alcohol

Abbreviations used are: A, alcohol; C/A, cocaine/alcohol; N.S., not significant. Values are mean ± S.D.; $n = 9$.

	A	C/A	P
C_{max} (μg/ml)	1276.6 ± 225.5	1127.9 ± 204.4	.04
T_{max} (min)	68.2 ± 20.4	71.2 ± 26.1	N.S.
$AUC_{(0-360)}$ (μg·min/ml)	269550.0 ± 56784.0	254916.2 ± 44910.9	N.S.

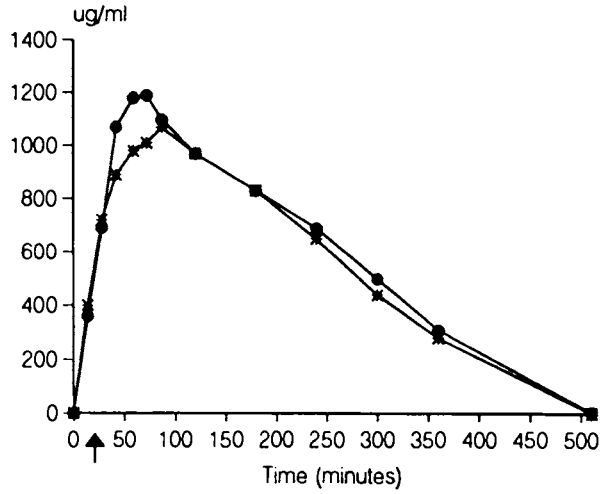

Fig. 4. Time course for mean ($n = 9$) blood alcohol levels of the two alcohol conditions (symbols as in fig. 1). The zero (0) time of the curve stands for the moment when alcohol administration started. The arrow signals cocaine administration.

found between the two conditions, with the peak occurring earlier in the drug combination condition. No differences were found in the elimination half-life values.

Plasma levels of BE were significantly higher in the COC condition than in the condition receiving the drug combination as reflected in the AUC_{0-480} (table 3, fig. 5). C_{max} values were also higher in the COC condition. No differences were found between conditions in the elimination half-life and T_{max}.

No differences were found in any of the pharmacokinetic parameters derived from EME plasma concentrations. Nevertheless, a similar trend of higher plasma levels in the COC condition as occurred with BE was also observed.

Plasma levels of NC in the drug combination condition were higher than in the COC condition as reflected in AUC_{0-480}, AUC_{total} and C_{max} values. Taking into account the high sensitivity reached in the assay for the quantification of NC, it should be noted that although NC was detected in all volunteers when receiving the drug combination, this substance was measurable only in six of the participants in the COC condition. In all participants, plasma concentrations of NC where higher in the drug combination condition.

The metabolite CE was present only in the condition receiving the drug combination. The plasma half-life of 99 min was slightly higher than that of 78 min for COC ($P < .0005$). When AUC_{0-480} of COC and CE were compared, plasma levels of CE accounted for about one-fifth of those calculated for COC.

There was a significant correlation between AUC of CE and AUC of COC and of BE ($r = 0.90$; $P < .01$) as well as between the elimination half-life of COC and of CE ($r = 0.96$; $P < .02$).

Time courses for mean plasma levels of COC, BE, EME, NC and CE are shown in figure 5.

TABLE 3

Pharmacokinetic parameters for cocaine and metabolites

Abbreviations used are: C, cocaine; C/A, cocaine/alcohol; N.S. not significant. Values are mean ± S.D.; $n = 9$.

Parameters	Cocaine			Benzoylecgonine			Ecgoninemethylester			Norcocaine			Cocaethylene
	C	C/A	P	C	C/A	P	C	C/A	P	C	C/A	P	C/A
C_{max} (ng/ml)	225.9 ±80.7	343.8 ±93.5	0.008	778.0 ±388.4	537.4 ±153.9	N.S.	129.8 ±80.8	86.2 ±44.5	N.S.	1.5 ±1.4	3.5 ±1.7	0.02	53.3 ±12.2
T_{max} (min)	58.2 ±18.1	37.9 ±16.9	0.04	213.3 ±112.6	186.7 ±59.6	N.S.	128.3 ±36.0	131.6 ±65.3	N.S.	130.0 ±74.5	107.0 ±54.5	N.S.	121.7 ±37.7
AUC (0–480)[a] (ng·min/ml)	38353.8 ±16190.1	54037.0 ±19152.8	0.008	239685.1 ±97405.0	165292.9 ±52922.1	0.01	30583.1 ±19855.1	22793.5 ±14446.4	N.S.	263.6 ±255.0	592.7 ±199.2	0.007	13331.8 ±4519.5
$t_{1/2\beta}$ (min)	79.8 ±28.7	78.0 ±22.5	N.S.	466.6 ±142.7	504.8 ±150.4	N.S.	147.8 ±39.8	197.1 ±122.4	N.S.	196.2 ±114.0	172.1 ±48.6	N.S.	99.1 ±23.9
$AUC_{(T_{\infty})}$ (ng·min/ml)	40577.0 ±17565.0	55559.0 ±21953.0	0.01	557695.0 ±249208.0	434357.0 ±177495.0	N.S.	40573.0 ±26731.0	35817.0 ±21867.0	N.S.	625.0 ±76.0	894.0 ±328.0	0.06	14517.9 ±5532.4

[a] AUC for norcocaine was calculated between 0 and 330 min.

Discussion

In the present study we obtained valuable information about the interactions between COC and alcohol and their effects on heart rate and blood pressure, subjective effects, psychomotor performance and pharmacokinetic parameters.

The alcohol dose (1 g/kg) used in this study produced characteristic effects in subjective and performance parameters. No significant changes were found in heart rate or blood pressure as compared with placebo. Alcohol-impaired psychomotor performance (increasing simple reaction time) diminished the number of correct responses in an arithmetical task and induced exophoria. These results are in agreement with observations made by other authors using similar methods of evaluation (Turkkan *et al.*, 1988; Heishman *et al.*, 1989).

The COC dose (100 mg snorted) used also produced some of the previously reported effects on subjective variables and heart rate and blood pressure using the same route of administration (Resnick *et al.*, 1976). COC increased heart rate and blood pressure. The increase in the heart rate observed had a duration of 1 hr, similar to that previously reported (Resnick *et al.*, 1976). Higgins *et al.*, (1990) have recently described an increase in heart rate during 3 hr after a single 96-mg dose of COC. This difference is probably due to repetitive performance testing (Foltin *et al.*, 1988).

COC increased subjective effects related to euphoria and well-being. In relation to psychomotor performance, COC increased the speed of decision time (alertness). The observation seems more relevant when some degree of fatigue is present (at the 90-min evaluation), at this time COC could help to reestablish the performance to baseline values. The results are in agreement with previous observations published by Higgins *et al.*, (1990) that COC can enhance psychomotor performance in rested subjects. Fischman and Schuster (1980) reported that COC only affected reaction time when administered to sleep-deprived subjects during 24 hr. In rested subjects, a trend for an improvement in reaction time was observed, although it was not statistically significant.

The combination of COC and alcohol produced a clinically significant increase in the heart rate when compared with placebo and COC. Increases in systolic and diastolic blood pressure were similar in the two conditions that included COC. These results are in accordance with a previous report using the combination of alcohol and COC (Foltin and Fischman, 1989). The magnitude of the changes observed in heart rate and blood pressure could have toxicologic consequences. Subjects using the drug combination could be at greater risk of cardiovascular complications than users of COC alone.

The simultaneous use of COC and alcohol produced more marked subjective effects than COC or alcohol alone. Although participants had the subjective feeling of a decrease in their degree of alcohol intoxication and an increase in COC-induced euphoria, differences were not statistically significant. The drug combination seems to produce a profile of more pronounced subjective effects than cocaine, with significant differences in ratings of some feelings related to well-being (feeling good, good effects). This observation could indicate that the combination of alcohol and COC would be more liable to abuse than alcohol or COC.

COC significantly improved performance impaired by alcohol in the simple reaction time test. Effects peaked at the 45 min evaluation (15 min after COC snorting). This observation could have relevance in driving situations and has not yet been described. The possible role of COC in driving impairment induced by alcohol should be further assessed in adequate driving simulation studies.

Blood alcohol levels were marginally lower in the first hour of the kinetics in the drug combination condition. Differences in the rate of alcohol absorption due to COC cardiovascular effects could explain this finding. The amount of alcohol involved in CE synthesis cannot account for the differences in ETOH levels.

With regard to the pharmacokinetics of COC, a relevant finding of the present study is that COC plasma levels were higher in those to whom alcohol was administered. This fact is supported by higher COC AUC and C_{max} in the drug combination condition. In contrast, AUC and C_{max} of BE and EME were lower in this condition. When combining these observations with the absence of differences in the COC elimination half-life and reduction by half of its plasma clearance, there is strong support for hypothesizing a metabolic inhibition in the metabolism of COC in the presence of alcohol. The maximal effect on COC metabolic inhibition is observed when alcohol reaches its C_{max}. The mechanism involved in this interaction remains unclear. Both the spontaneous and enzymatic hydrolysis of COC (Inaba *et al.*, 1978; Inaba, 1989; Dean *et al.*, 1991) are partially inhibited in the presence of alcohol. In the case of spontaneous hydrolysis (leading to BE), it has been reported that this process can be altered *in vitro* by changes in the environmental pH (Baselt, 1983; Isenschmid *et al.*, 1989). Nevertheless, despite the fact that metabolic acidosis has been described in acute alcohol intoxication (Rumack *et al.*, 1986), it seems unlikely that small changes in blood pH could be responsible for the differences observed. Two recent reports suggest that hepatic nonspecific carboxylesterase is involved in the degradation of COC to BE (Dean *et al.*, 1991; Boyer and

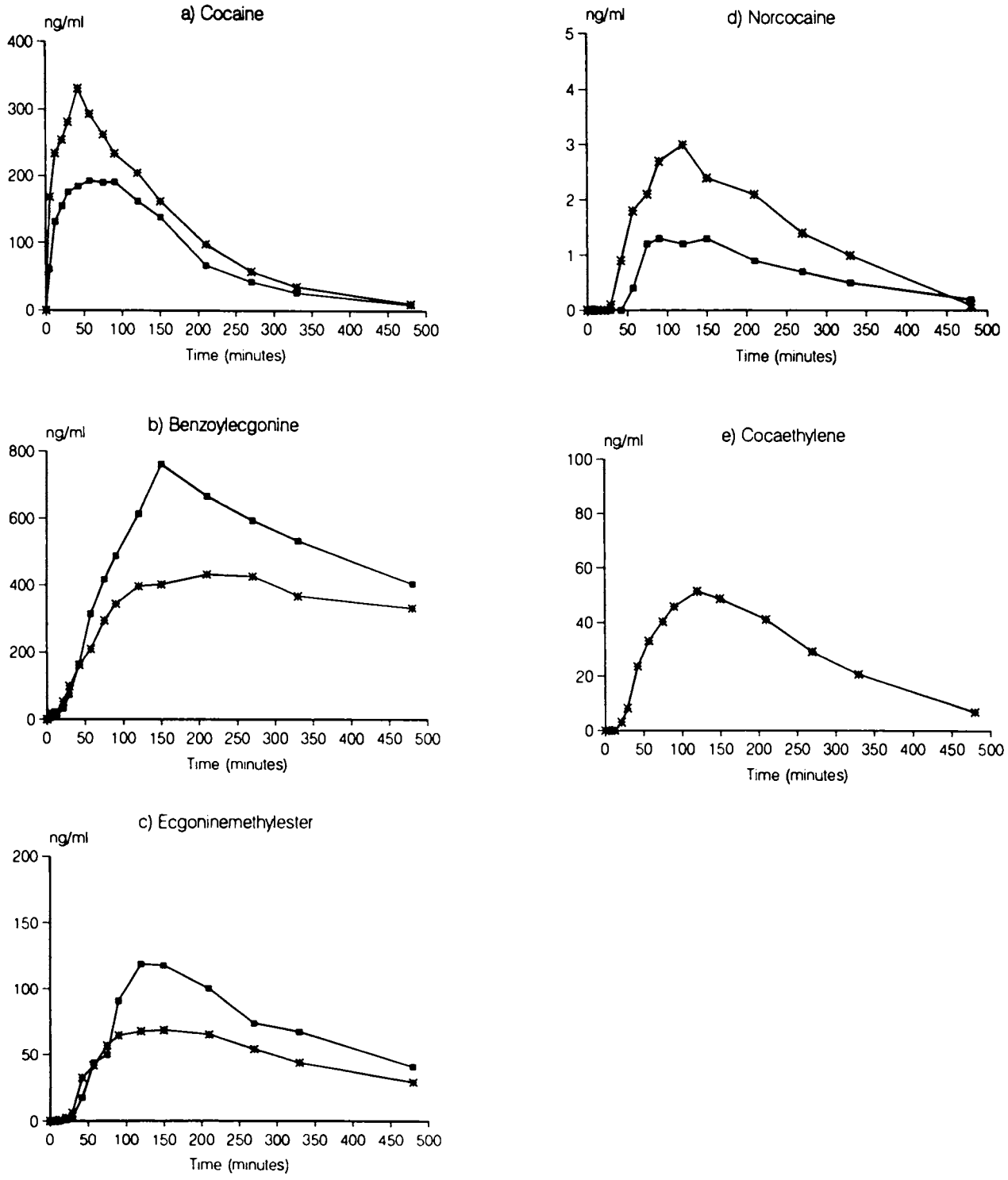

Fig. 5. Time course for mean (n = 9) plasma concentrations of (a) cocaine, (b) benzoylecgonine, (c) ecgoninemethylester, (d) norcocaine and (e) cocaethylene in the two cocaine conditions. Symbols as in figure 1. The zero (0) time of these curves stands for the moment when cocaine were administered.

Petersen, 1992). The same enzyme catalyzes the transesterification of COC to CE in the presence of alcohol. If both metabolic reactions are regulated by the same enzyme, it may be proposed that a competitive mechanism would explain our findings with regard to BE plasma levels.

A small difference (20 min) in COC T_{max} has been detected with the absorption of COC being faster in the drug combination condition. This fact could point to a vasodilation of the nasal mucosa because of the presence of alcohol. On the other hand, an increased bioavailability of COC in the presence of alcohol may be suggested. The sum of AUC_{0-480} of COC and its main metabolites, as an index of the total bioavailability of COC, does not show substantial differences between the drug combination condition and COC alone (256048 *vs.* 308886 ng·min/ml). The relevance of the slight difference observed in absorption rate is then meaningless when compared with the

metabolic interaction previously discussed. Moreover, the high rate of hepatic extraction of COC prevents any significant modification of its body clearance as a result of the diuretic effect of alcohol. The results obtained do not, therefore, seem to support renal impairment.

The kinetics of NC in plasma is one of the first described in humans, and has been made possible thanks to the high sensitivity and specificity of the assay used. The method developed is based on previous studies for the urinalysis of COC in drug screening testing (Ortuño *et al.*, 1990).

A major finding has been that NC plasma levels in the drug combination condition almost doubled those encountered in the COC condition, as reflected in C_{max} and AUC values. As has been stated previously, it is again worth pointing out that, although in the COC condition the plasma levels of NC in three volunteers were below the detection limit of the analytical technique, NC was detected in all the volunteers in the drug combination condition. An isozyme of the cytochrome P_{450} is responsible for the COC-N-demethylation to NC (Kloss *et al.*, 1983). It seems probable that increased availability of the substrate for this metabolic reaction, *i.e.*, higher levels of COC in the drug combination condition, would be responsible for the higher levels of NC observed. No inhibitory effect of alcohol on cytochrome P_{450} has been observed for COC-N-demethylation in contrast to some reports for other metabolic reactions with other drugs (Sandor *et al.*, 1981). The reduction in the time lag observed for the detection of NC in the drug combination condition is in agreement with differences observed for COC T_{max} and support the previous hypothesis.

COC can be responsible for hepatotoxicity in laboratory animals and in man (Shuster *et al.*, 1988). A metabolic activation of COC *via* NC by multiple oxidative steps mediated by cytochrome P_{450} seems to be necessary to obtain hepatotoxic responses (Rauckman *et al.*, 1982; Shuster *et al.*, 1983). Although the plasma levels of NC are low, their hepatotoxicity deserve further studies. Furthermore, the differences observed in NC concentrations between COC and the drug combination conditions could give support to observations of an increased hepatotoxicity of COC when coadministered with alcohol in laboratory animals (Boyer and Petersen, 1990).

The detection of plasma concentrations of CE in healthy volunteers confirms preliminary results in urine (de la Torre *et al.*, 1991) on the relevance of this active metabolite when COC and alcohol are concurrently given. In most of the previous studies, CE has been detected in acute COC intoxications or in fatal casualties where alcohol was present (Rafla and Epstein, 1979; Jatlow *et al.*, 1991). The present study shows that CE can be generated at doses compatible with the recreational consumption of COC and alcohol. It has been suggested that CE is generated by a transesterification of COC in the presence of alcohol (Hearn *et al.*, 1991; Dean *et al.*, 1991). We studied the correlation between AUC of CE and those of COC and BE in order to relate these two hypothetic substrates of CE with to possible metabolic reactions: transesterification of COC or esterification of BE. Our results of a significant correlation between AUC of CE and AUC of COC and of BE support the metabolic pathway of transesterification of COC to CE in the presence of alcohol.

The findings presented in this study are the first description of the pharmacokinetics of CE in man, and should be considered when interpreting results of COC and alcohol coadministration. The values for the pharmacokinetic parameters may well be slightly different in the case of direct administration of synthetic CE to humans. The observation that the elimination half-life of CE is slightly greater than that calculated for COC can be explained by differences in the liposolubility of both substances. There was a good correlation between the elimination half-life of COC and CE suggesting that both substances share the same clearance process. Based on the pharmacologic profile of CE (Hearn *et al.*, 1991; Jatlow *et al.*, 1991), it is tempting to speculate that this substance may be partially responsible for more substained effects of COC in its interaction with alcohol.

The increase in the pharmacologic effects of COC when given simultaneously with alcohol could be related to higher COC plasma levels in the drug combination condition. However, changes observed seem lower than those expected on a quantitative basis considering that the sum plasma levels of COC and its active metabolites (CE and NC) in the drug combination condition almost doubled those found in the COC condition. This could be explained by the development of acute tolerance to the effects of COC (Chow *et al.*, 1985; Ambre *et al.*, 1988).

In conclusion, subjects taking recreational doses of alcohol and COC simultaneously experienced subjective and performance effects that can be self-interpreted as more pleasant compared to the effects of alcohol alone. However, the coadministration of these drugs gives rise to the presence of CE and higher levels of COC and NC in plasma. These changes could contribute to the increased toxicity of the drug combination in comparison with the effects of both drugs taken separately.

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