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Cocaine Metabolism in Humans after Use of Alcohol

Clinical and Research Implications

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Abstract. The simultaneous administration of cocaine and alcohol implies a pharmacological interaction at pharmacodynamic and pharmacokinetic levels. The latter involves an alteration of cocaine kinetics and metabolism, as well as the biosynthesis of newly active metabolites, such as cocaethylene. Cocaethylene is metabolized along the same pathways as cocaine. Its detection in biological samples indicates the combined consumption of cocaine and alcohol. From epidemiological and toxicological data, it has been suggested that the combination of alcohol and cocaine produces an increased toxicity in addition to behavioral changes. There has been some debate regarding the contribution of cocaethylene to this rise of toxicity. Its pharmacological and toxicological profile is very similar to cocaine. During the interaction of both substances, the rise in cocaine plasma concentrations can explain many of cardiovascular and behavioral effects observed. The contribution of cocaethylene to the interaction is probably minor; its effects are likely additive to those of cocaine. Perhaps its longer elimination half-life can help in understanding long-lasting effects of the alcohol–cocaine combination.

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1. Cocaine and Alcohol Consumption: Epidemiological and Toxicological Data

1.1. Epidemiological Data

The simultaneous use of cocaine and alcohol is very common. In the 1985 national survey on drug abuse done in the United States, prevalence rates for the simultaneous use of alcohol and cocaine (defined as the use of both drugs at the same time or within 2 hr) were 2.4% for the past month and 4.7% for the past year. Population estimates associated with these figures might suggest that 4.5 million Americans are using this drug combination each month.[1]

Recent data seem to indicate that a large proportion (64%) of patients who reported simultaneous cocaine and alcohol use most of the time (more than 50%) when using cocaine met criteria for alcohol dependence.[2] In a sample of 212 problem drinkers who participated in an alcohol treatment program, the prevalence of polydrug use was investigated, particularly the use of alcohol and other drugs in combination or on the same day. The majority of subjects (61%) reported simultaneous polydrug use. The most frequent alcohol–drug combination was alcohol with cocaine (60% of subjects reporting polydrug use) followed by alcohol with marijuana (51%) and alcohol and sedatives (31%).[3]

It appears that important differences could be found between cocaine-dependent subjects and subjects who fulfill criteria for both cocaine and alcohol dependence. Cocaine–alcohol-dependent persons had higher depression and global severity scores and were more likely to experience paranoid psychosis with cocaine use and to abuse of additional substances. The combination-dependent subjects attended fewer therapeutic sessions. These features suggest that these patients could require a more intensive treatment.[4] It has been described that simultaneous use of alcohol and cocaine contributed to a high prevalence of violent behavior. Patients using both substances had a higher likelihood of associated current homicidal behavior than cocaine-only and alcohol-only abusers.[5]

Cocaine abusers reported that the administration of alcohol produced an increase both in magnitude and duration of some of the euphoric effects of cocaine, and additionally a reduction of some of the unpleasant symptoms associated with the warning of cocaine effects ("crash").[6] In an interesting study on drug preference, it has been demonstrated that alcohol pretreatment significantly increased choice of cocaine versus placebo in nondependent cocaine users. Ratings of pleasurable-related effects and cardiac output were higher in those subjects who chose cocaine and were pretreated with ethanol as compared with those who selected cocaine but did not receive alcohol.[7]

1.2. Toxicological Data

The use of cocaine has been related to the appearance of social problems, mainly related to violent behaviors, including homicides, suicides, and acci-

dents. The use of cocaine and alcohol seems to increase the risks of medical and legal complications.

In forensic studies, cocaine and ethanol are frequently identified in biological samples from fatally injured drivers.[8,9] and in homicide victims.[10] In a sample of driver fatalities, it was found that almost one of four drivers had used cocaine within 48 hr of death. Fifty-six percent of all drivers killed in fatal traffic accidents had cocaine metabolites, alcohol, or both detected at autopsy. In 10% of all fatalities, cocaine metabolites and alcohol were found.[8]

In a study designed to assess the presence of different drugs of abuse in 2824 homicide victims, cocaine or benzoylecgonine were found in 31.3% of victims, cocaine–benzoylecgonine without other drugs in 13.4%, cocaine–benzoylecgonine with ethanol in 10.6%, cocaine–benzoylecgonine with opiates in 7.3%, alcohol alone in 21.1% and opiates alone in 2%.[10]

A group of 325 cocaine abusers seen in an emergency room was divided into those who screened positive for benzoylecgonine ($n = 190$) and those positive for benzoylecgonine and alcohol ($n = 135$). Patients positive for both drugs were more frequently involved in violent trauma and presented higher heart rate and blood pressure levels on admission than cocaine-only-positive patients. Two subjects with myocardial infarction were positive for both drugs, but the incidence of rhabdomyolysis was lower in this group of patients.[11]

Cocaethylene, as a marker of simultaneous cocaine and ethanol use,[12] was detected in 25% of patients examined in a hospital emergency room who had positive urines for benzoylecgonine in a urinary screening for drugs of abuse.[13] In a sample of 416 trauma patients, urine was tested for the presence of benzoylecgonine. A total of 158 (38%) subjects tested positive for this metabolite. In 114 of these patients, a blood sample was obtained in order to determine cocaine, cocaethylene, and ethanol. Cocaethylene was detected in blood samples in 60% of tested patients, with a mean concentration of 41 ng/ml (range 3 to 213 ng/ml). All patients tested positive for cocaine, with a mean concentration of 92.9 ng/ml (range 3.8 to 699.9 ng/ml), but only 56% were positive for ethanol. The results suggest that cocaethylene could be present in more than half of the subjects who tested positive for cocaine (more precisely, benzoylecgonine present in urine samples).[14]

2. Cocaine and Alcohol Interactions in Humans

2.1. Pharmacological Effects of the Cocaine and Alcohol Combination

The effects of the combination of cocaine and ethanol in healthy volunteers have been assessed in a number of studies, all of which included the evaluation of subjective and physiological effects; several studies presented data on the pharmacokinetics of cocaine and its metabolites, including cocaethylene.[6,15-18]

Summarizing the results of these studies, it seems that the administration of cocaine in subjects who had consumed social-like doses of ethanol pro-

duced an enhancement or an antagonism of some of the characteristic effects of each drug. The combination of both drugs induced a significant increase in euphoriclike effects ("high," "good effects," "liking") and caused a clinically significant increase in the cardiovascular effects of cocaine with a very important rise of heart rate and blood pressure. Cocaine also antagonized in part some of the deleterious effects of alcohol, producing lower ratings of drunk feelings and an amelioration of some psychomotor performance tasks altered by alcohol. Subjects performed better under the drug combination condition than under the use of alcohol alone but significantly worse than under placebo or cocaine alone.[17,19] At the neuroendocrine level, the drug combination induced an increase in cortisol levels[19] that was greater than that observed after cocaine administration. Cocaine alone seems to decrease serum prolactin levels,[20] which is in contrast with that reported for ethanol. However, the administration of cocaine did not change the increase in prolactin induced by the administration of alcohol.[19]

2.2. Pharmacokinetics of the Cocaine–Alcohol Interaction

In several clinical trials in healthy volunteers, where different doses of alcohol and cocaine were coadministered, similar pharmacokinetic results have been observed.[6,16,18,19]

Plasma levels of cocaine in the drug combination condition were higher than in the cocaine-only condition, and cocaine plasma clearance was reduced by one half. No differences were found in the elimination half-life values.

Plasma levels of benzoylecgonine were significantly higher in the cocaine condition than in the drug combination condition. No differences were found between conditions in the elimination half-life and in any of the pharmacokinetic parameters derived from ecgonine methyl ester plasma concentrations. Plasma levels of norcocaine in the drug combination were higher than in the cocaine condition.[6,19]

The metabolites cocaethylene and norcocaethylene were present only in the condition receiving the drug combination. When the area under the curve (AUC) of cocaine and cocaethylene were compared at 0 and 8 hr, plasma levels of cocaethylene accounted for about one fifth of those calculated for cocaine. No significant differences were observed in the alcohol pharmacokinetics.[6,19]

In summary, cocaine plasma concentration are higher in the combination conditions. However, benzoylecgonine plasma concentrations are lower in the same condition. Combining these observations with the absence of differences in cocaine elimination half-life and reduction by half of its plasma clearance, there is strong support for the hypothesis of a metabolic inhibition in the metabolism of cocaine in the presence of alcohol. Cocaine is metabolized to benzoylecgonine by spontaneous hydrolysis in plasma and by the action of a hepatic nonspecific carboxylesterase.[21,22] In the presence of ethanol, this enzyme is responsible for the transesterification of cocaine, forming
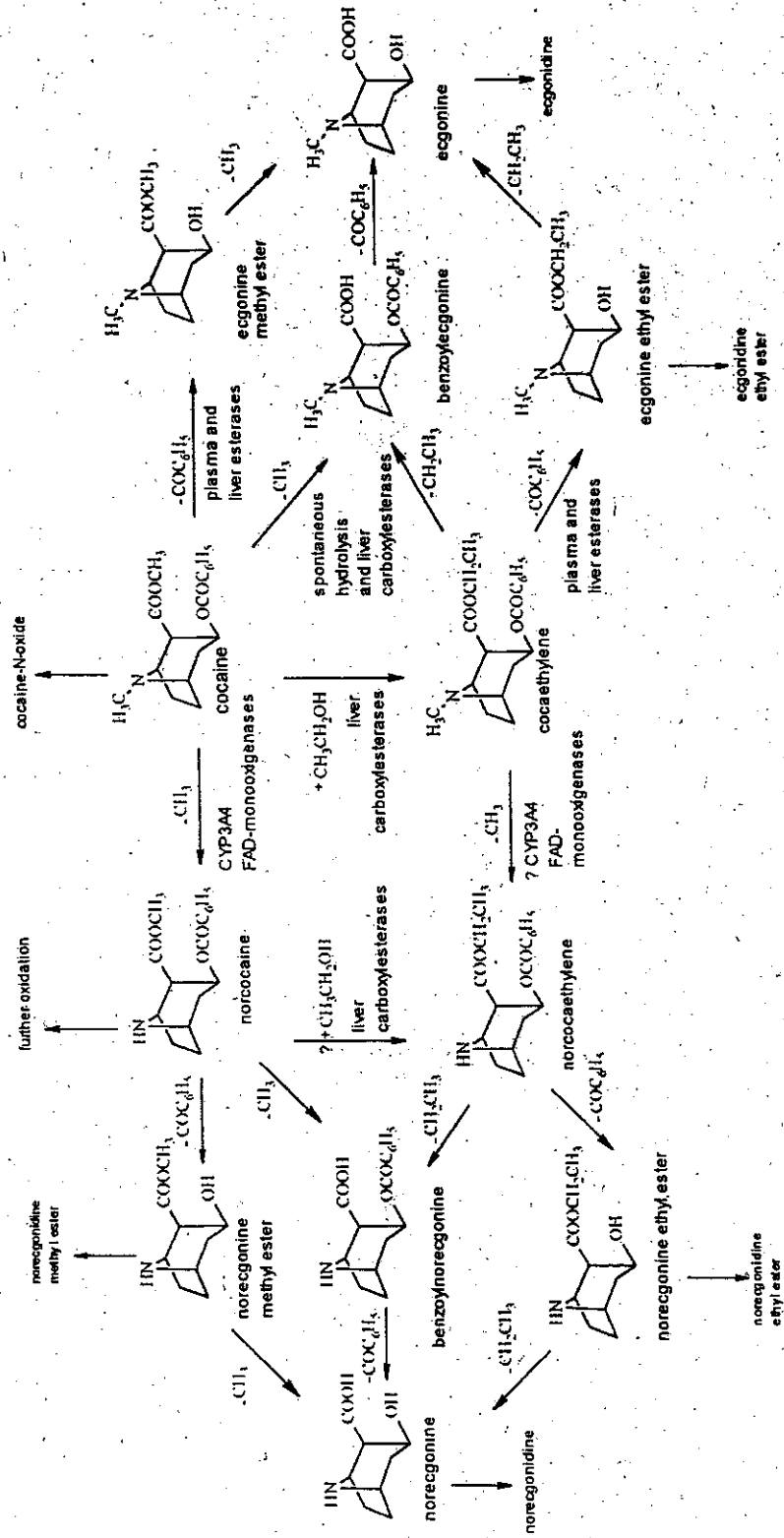
Figure 1. Cocaine and cocaethylene metabolic pathways.

the active metabolite cocaethylene.[23,24] Some of the pharmacokinetic findings could be explained by a competitive mechanism between both substrates, since the same enzyme regulates both metabolic pathways. Cocaine and co-caethylene metabolic reactions are summarized in Fig. 1. The order of drug administration could be a crucial factor in this interaction. In one study, no differences in cocaine plasma concentrations were observed when alcohol was administered 30 min after cocaine snorting.[25]

3. Cocaethylene

Cocaethylene (benzoylethylcocaine) is a pharmacologically active metab-olite of cocaine initially found in cases of cocaine and ethanol intoxication.[12,26] It has been identified in plasma and urine of healthy volunteers,[6,27] as well as in postmortem samples from trauma victims.[28-30] Cocaethylene has been found in urine, blood, and tissues of subjects who consumed cocaine and alcohol simultaneously. Recent reports have documented the presence of high levels of cocaethylene in blood samples of patients who had recently ingested cocaine and ethanol. In some cases, concentrations of cocaethylene were higher than those of cocaine. In a series of 41 patients, the ratio of cocaethylene–cocaine concentrations in plasma showed a mean value of 1.3, ranging from 0.1 to 4.7.[30]

3.1. Basic Pharmacology

Cocaethylene has a pharmacological profile similar to that of co-caine.[29,31-33] It displays equal affinity for the dopamine transporter as cocaine. It also blocks dopamine uptake at the presynaptic level, increasing concentra-tions of dopamine in the synaptic cleft. Apparently, cocaethylene is a more selective indirect dopamine agonist, as it is a lesser inhibitor of serotonine uptake than cocaine. In animal models, cocaethylene increases locomotor activity and it is self-administered by nonhuman primates.

3.2. Pharmacological Effects of Cocaethylene in Humans

There are three published studies where cocaethylene was administered by different routes (intravenous or intranasal) to evaluate its pharmacological effects in comparison with those of cocaine.

In a pilot study[34] that included three male recreational users of cocaine, cocaethylene was administered at doses of 0.025, 0.05, 0.1, 0.15, 0.20, and 0.25 mg/kg by the intravenous route (as a bolus during 1 min). After that, the same subjects were given an intravenous injection of cocaine (0.25 mg/kg). In the case of cocaethylene, no effects on subjective or cardiovascular parame-ters were reported for doses below 0.15 mg/kg. The subjective effects, de-scribed as increases in the feelings of arousal, pleasure, and increased energy,

rated more intensely in a dose-dependent manner. These feelings were stronger at 0.25 mg/kg dose. Also, a dose–response effect was observed on heart rate (30% increase from baseline at the highest dose), but minimal changes were observed on blood pressure. In comparison to cocaine, cocaethylene produced tachycardic effects of similar magnitude, and subjects judged the effects of cocaethylene as more pleasant but less intense than those produced by cocaine.

In a single-blind, cross-over study,[35] six male recreational users of cocaine were given intravenous injections of cocaine (0.25 mg/kg as a cocaine base) and cocaethylene (0.25 mg/kg as a cocaethylene base). Several variables were collected over a period of time including subjective effects ("high"), cardiovascular parameters (heart rate, blood pressure), and blood samples to measure cocaine and cocaethylene. The results showed that cocaethylene was less potent than cocaine, producing changes of lower magnitude in "high" feelings (65%) and heart rate (43%) as compared with cocaine.

In a third study,[36] eight male cocaine abusers (mean dose 3.6 g/week) who were not seeking treatment participated in four experimental sessions. One of the following drugs by intranasal route was given in each session: cocaethylene (0.48 or 0.95 mg/kg), cocaine (0.92 mg/kg), or placebo (lactose, 1 mg/kg). Different variables were measured at baseline and after drug administration. These included different self-rated visual analogue scales ("high," "pleasant", etc) and physiological measures (heart rate, blood pressure). Blood samples were obtained to determine the concentrations of cocaine and cocaethylene. Cocaethylene 0.95 mg/kg and cocaine produced similar effects on "high" rating, but peaks were observed some minutes later in the cocaethylene condition (15 vs. 30 min). Subjects were unable to distinguish between both conditions. With regard to cardiovascular parameters, similar effects on heart rate and blood pressure were recorded, but after cocaethylene administration these effects peaked later. The effects induced by the lowest cocaethylene dose were significantly lower than those induced by cocaine and the highest cocaethylene dose. As a summary, equimolar doses of cocaine and cocaethylene produced similar subjective and cardiovascular effects.

3.3. Pharmacokinetics of Cocaethylene

Most of the pharmacokinetic parameters of cocaethylene derive either from two experiments[35,36] in humans, where this substance was administered by the intranasal and the intravenous route at different dose levels, or from studies of cocaine alcohol interaction.[6,19] While studies that administer pure cocaethylene are more suitable for the estimation of pharmacokinetic parameters, it is closer to the real situation to evaluate it in the context of the concomitant consumption of alcohol and cocaine. In experimental studies in volunteers using social doses of both cocaine and ethanol, the concentrations of cocaethylene were lower than those of cocaine. The ratios of peak concentrations or AUC between both substances, seems to be around 15–25%.[6,19] Table

I summarizes pharmacokinetic parameters of cocaethylene in both situations. Pharmacokinetic parameters of cocaine calculated for each experiment have been included as a "control" group for better comparison with those estimated for cocaethylene. There is good agreement between experiments on pharmacokinetic parameters either for cocaine or cocaethylene. The main differences between both drugs are related to their body clearence. Cocaethylene appears to be eliminated more slowly than cocaine, and thus might be expected to accumulate during a binge, which is consistent with analyses of forensic and clinical samples.[37] Differences observed in plasma half-lifes[38] between cocaine and cocaethylene may be explained because of renal tubular reabsorption of cocaethylene. This observation is most probably related to the higher hydrophobicity of cocaethylene as compared with cocaine.

Norcocaethylene, an N-demethylated product of cocaethylene, has also been detected in plasma and urine of subjects given alcohol and cocaine concomitantly. Its estimated elimination half-life is 162 ± 59 min, which is greater than that of norcocaine (110 ± 29 min).[19]

Urinary recoveries (24 and 48 hr) for cocaethylene and norcocaethylene are presented in Table II. Urinary excretion rates are presented in Fig. 2. One interesting finding that deserves further research is that recovery of oxidative products like norcocaine in addition to norcocaethylene in the combination groups is higher (100%) than in the cocaine groups. It is unclear whether this observation is a direct effect of alcohol on liver metabolism or a larger availability of substrate (i.e., cocaine), because of metabolic inhibition, for oxidation. In addition, and based on plasma AUC ratios between cocaethylene and norcocaethylene and urinary recoveries, there is apparently an increase in oxidative metabolism of cocaethylene as compared with cocaine. Table III summarizes cocaine and metabolite urinary concentrations in subjects (n = 48) testing positive for cocaine metabolites by fluorescence polarization immunoassay (FPIA) in a noncontrolled setting. Subjects were not overdose or trauma victims but were a population of heroin addicts (n = 354) consuming cocaine concomitantly. Samples testing positive for cocaine by FPIA were reanalyzed by gas chromatography/mass spectrometry (GC/MS).[39] Among other substances, cocaethylene was detected in a 71% of cocaine-positive tested samples (34 of 48).

3.4. Cocaethylene and Cocaine Metabolism

What is known about cocaethylene metabolism is quite close to cocaine (see Fig. 1). In summary, cocaine is extensively metabolized in humans and only a small percentage is excreted unaltered in urine.[22,40,41] Cocaine is rapidly metabolized to ecgonine methyl ester by plasma and liver cholinesterases.[23,42-44] Cocaine is also spontaneously hydrolyzed in plasma to benzoylecgonine[22,44] and also by a recently identified human liver carboxylesterase.[23,24] Both are known as the main metabolites excreted in urine. The percentage of these metabolites found in plasma depends on the

Table I. Cocaethylene Pharmacokinetic Parameters in Humans

Study/drug	Dose	Admin. route	$t_{1/2a}$ (min)	$t_{1/2}$ (min)	t_{max} (min)	C_{max} (ng/ml)	V (liter)	CL (liter/min/kg)
McCance[36]								
Cocaine	0.92 mg/kg	Snorting	17.0	111.0	64.0	144.0		
	0.48 mg/kg	Snorting	10.0	155.0	43.0	128.0		
Cocaethylene	0.95 mg/kg	Snorting	13.0	138.0	41.0	251.0		
Perez-Reyes[35]								
Cocaine	0.25 mg/kg	IV		64.2		170.3	205.0	133.0
Cocaethylene	0.25 mg/kg	IV		100.8		159.6	211.0	86.0
Farré[6]								
Cocaine	100 mg	Snorting		78.0	37.9	343.8	229.0	
Cocaethylene[a] (cocaine/alcohol)	100 mg/1 g/kg	Snorting		99.0	121.0	53.3		
Farré[20]								
Cocaine	100 mg	Snorting	14.7	76.1	41.3	330.5	270.0	
Cocaethylene[a] (cocaine/alcohol)	100 mg/0.8 g/kg	Snorting		113.2	116.0	48.7		

[a]Cocaethylene derived from the interaction of cocaine and alcohol

Table II. Urinary Recoveries of Cocaine and Cocaethylene in Healthy Subjects[a]

Compound	Recovery (μmole)[b]		Recovery (%D)	
	C	C/A	C	C/A
A. Urinary excretion recovery at 24 hr of cocaine and its main metabolites in healthy volunteers ($n = 7$) after the simultaneous use of cocaine intranasal (100 mg) and ethanol (1 g/kg)				
Cocaine	5.6 ± 3.1	11.7 ± 4.3	1.9 ± 1.1	4.0 ± 1.4
Benzoylecgonine	72.3 ± 16.4	59.0 ± 15.6	24.6 ± 5.7	20.1 ± 5.3
Ecgonine methyl ester	66.8 ± 38.9	66.7 ± 25.8	22.7 ± 13.22	22.7 ± 8.8
Cocaethylene	ND	1.9 ± 0.6	ND	0.6 ± 0.2
Norcocaine	0.65 ± 0.26	1.34 ± 0.52	0.22 ± 0.09	0.46 ± 0.18
Total	145.35	140.64	49.42	47.86
B. Urinary excretion recovery at 48 hr of cocaine and its main metabolites ($n = 6$) after simultaneous use of cocaine intranasal (100 mg) and ethanol (0.8 g/kg)				
Cocaine	2.9 ± 0.8	9.4 ± 2.5	0.9 ± 0.2	3.2 ± 0.8
Benzoylecgonine	89.0 ± 17.9	84.0 ± 18.9	30.2 ± 6.1	28.5 ± 6.4
Ecgonine methyl ester	67.0 ± 14.2	73.9 ± 13.4	22.8 ± 4.8	25.1 ± 4.6
Cocaethylene	ND	2.1 ± 0.8	ND	0.7 ± 0.3
Norcocaine	0.19 ± 0.08	0.34 ± 0.13	0.06 ± 0.03	0.12 ± 0.04
Norcocaethylene	ND	0.18 ± 0.08	ND	0.06 ± 0.00
Total	159.09	169.92	53.96	57.68

[a]The results are expressed as μmole (mean ± standard deviation) and the percentage of the dose (D, 294.3 μmole of cocaine base).
[b]C, cocaine group; C/A, combination group; ND, not detected.

administration route. In human studies carried out after intranasal administration of doses of 2 mg/kg[-1] of cocaine, plasma concentrations of ecgonine methyl ester were about one third of those of benzoylecgonine.[45] When cocaine was smoked or injected, the concentrations of ecgonine methyl ester were lower (about 5% of those of benzoylecgonine).[46,47]

Norcocaine is a N-demethylated minor active metabolite of cocaine in humans (between 2 and 6% of the dose)[21] produced by liver isoenzymes of the cytochrome P450 (CYP3A)[48,49] and also through FAD mono-oxygenases, which form first the N-oxide of cocaine and then it is N-demethylated by the action of the cytochrome P450 to form norcocaine.[50-53] The subsequent oxidation of norcocaine has been associated with hepatotoxicity derived from cocaine consumption in experimental animal models[52,54-56] and also in humans.[57,58]

Cocaethylene is formed by the interaction between cocaine and ethanol. The human liver carboxylesterase recently identified[23,24] is responsible not
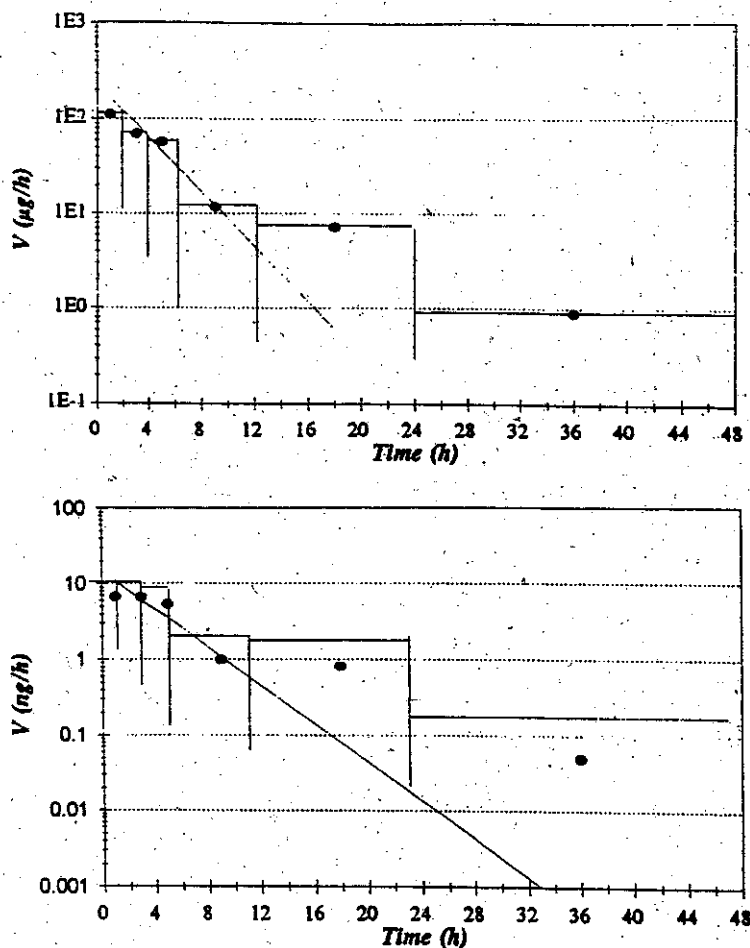
Figure 2. Urinary excretion rates of cocaethylene (upper) and norcocaethylene (lower) in a collection period 0–48 hr after the simulatneous use of cocaine 100 mg and ethanol 0.8 mg/kg.

only for the hydrolysis of cocaine to benzoylecgonine but also of cocaethylene formation by ethyl transesterification of cocaine in the presence of ethanol. It also has been shown that cocaethylene is not formed from benzoylecgonine by transesterification.[23,32] Recently, it has been reported that the enzyme responsible for the esterification of fatty acids in the presence of ethanol can also produce cocaethylene from cocaine.[59] Cocaethylene seems to be metabolized to benzoylecgonine and ecgonine ethyl ester in the same way as cocaine. The corresponding N-demethylated metabolite of cocaethylene (equivalent to norcocaine for cocaine), norcocaethylene, is present in plasma and urine of individuals using cocaine and alcohol concurrently.[19,39]

Table III. Urinary Cocaine and Metabolite Concentrations in Heroin Addicts Concomitantly Using Cocaine

Substance	Cocaine	Benzoylecgonine	Ecgonine methylester	Cocaethylene	Norcocaine	Norcocaethylene
Median (μg/mL)	0.098	3.44	0.47	0.15	0.032	0.022
Range	0.009–20.72	0.042–424.71	0.038–112.28	0.007–7.94	0.006–2.6	0.016–0.052
n^a	46	48	33	34	27	3

[a]Refers to the number of urines testing positive for a particular substance. Total number of urines analyzed = 48.

There also are some other minor metabolites of cocaine, such as methyl ecgonidine derivatives, the corresponding ethyl derivatives of which are present in urines of individuals who are concomitant consumers of cocaine and alcohol.[39] Nevertheless, it is still controversial whether these compounds are degradation products from dehydration reactions occurring either in the process of smoking (crack)[60,61] or during the analysis of biological fluids by gas chromatographic techniques,[62] or whether they are real metabolites of cocaine and cocaethylene. Urinary metabolic profiles of cocaine administered alone or concomitantly with alcohol are shown in Fig. 3.

3.5. Cocaethylene Toxicity

Cocaethylene toxicity is a controversial issue. The combination of cocaine and ethanol has shown higher toxicity compared with the administration of cocaine and ethanol alone.[63,64] It is unclear what is the contribution of cocaethylene to this general observation. Some reports suggested that cocaethylene was more potent than cocaine in mediating lethality.[65] There are several studies that suggest that it can be more hepatotoxic than cocaine.[65] However, some clinical studies do not seem to support data found in in vitro studies and in animal models. For example, hepatotoxicity is not increased in alcoholics with positive urinary cocaine metabolites. Alcoholics abusing cocaine do not have a larger prevalence of severe hepatotoxicity; in those cases where it is observed, it may represent comorbidity.[66] Several clinical studies have described an increase in cocaine oxidative metabolism. In particular, cocaethylene seems to be oxidized to norcocaethylene in a larger proportion to what is observed for cocaine. Its significance in terms of hepatotoxicity is still unknown.[6,19] In addition, animal models seem to support that cocaine-induced liver injury appears to be reversible.[67]

Cocaethylene shows similar immunotoxicity to that associated with cocaine,[68] and especially to N-demethylated metabolites (norcocaine and norcocaethylene and their rise during cocaine–alcohol interaction), which are potentiated by ethanol.[69] This observation is not surprising, since cocaine (cocaethylene) immunotoxicity is related to cytochrome P450 activation by cocaine.[70]

Cocaethylene is as cardiotoxic as cocaine, but it is less toxic than cocaine plus ethanol, probably because of the pharmacological interaction; in fact, cocaine at the same doses produced similar effects to cocaethylene.[71] It has been reported to reduce cardiac function in a dose-dependent manner and may be responsible for the delayed but substantial cardiotoxicity that occurs in individuals who use both cocaine and alcohol.[72]

Most probably, the increased toxicity in those individuals who combine cocaine and alcohol compared with that observed for these drugs abused alone is due to increased cocaine plasma concentrations; this is most likely because the metabolic interaction described previously is marginally related to cocaethylene. There also are several other factors that are involved, such as
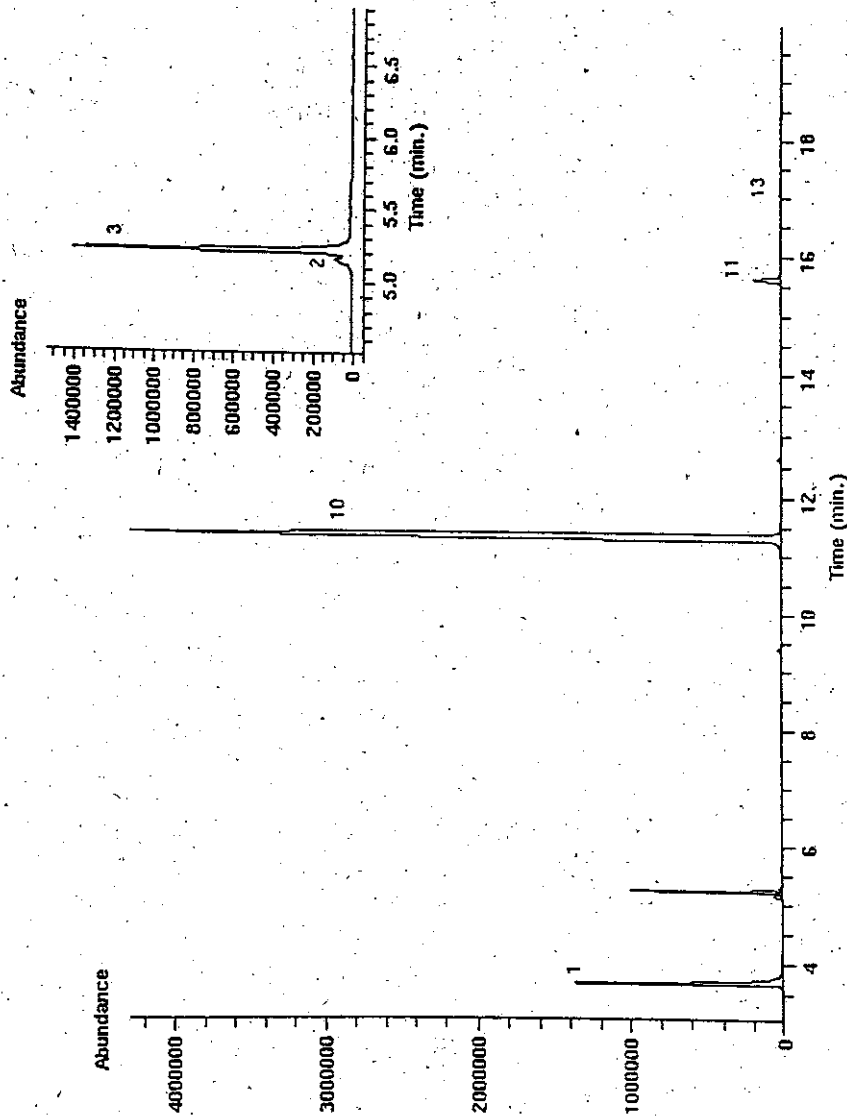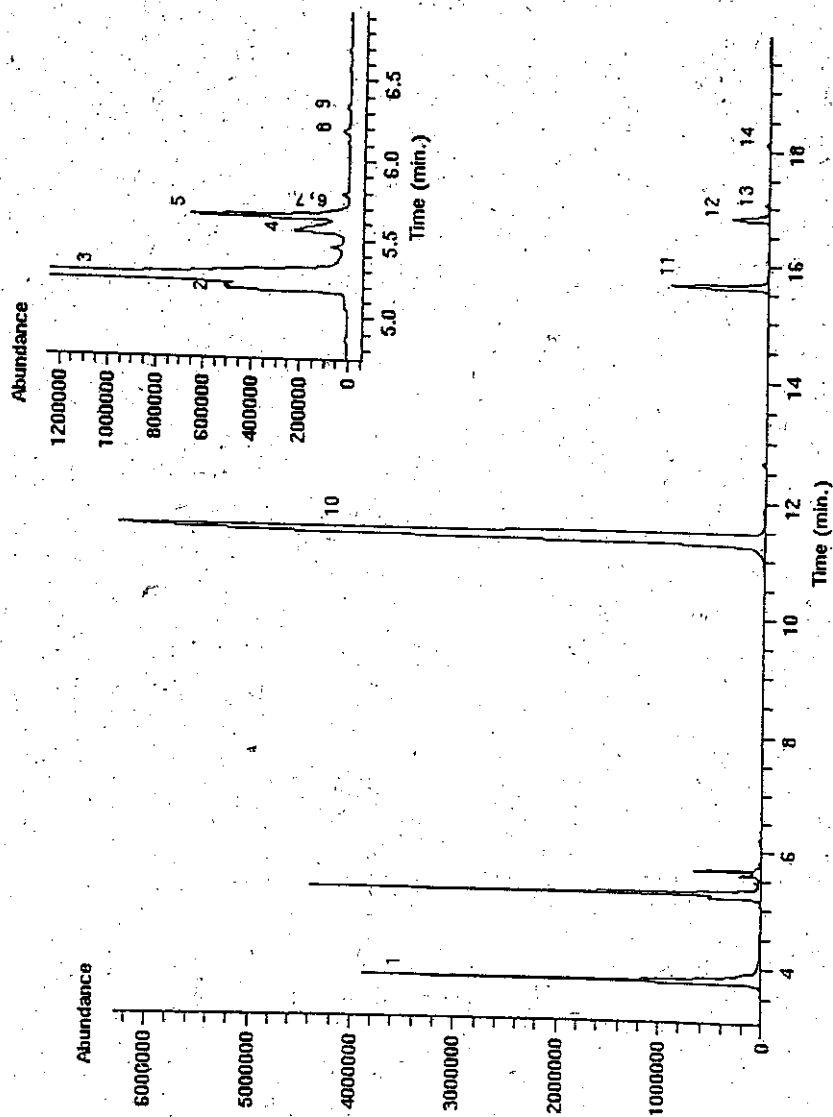
Figure 3. Total ion current profile (SIM acquisition mode) from the GC/MS analysis of a derivatized urine from a healthy volunteer who consumed cocaine (A) alone and (B) cocaine and alcohol. (1) COO-HFIP-ecgonidine; (2) ecgonidine methyl ester; (3) O-PFP-ecgonine methyl ester; (4) ecgonidine ethyl ester; (5) O-PFP-ecgonine ethyl ester; (6) N-PFP-norecgonidine methyl ester; (7) N,O-bis-PFP-nor-

ecgonine methyl ester; (8) *N*-PFP-norecgonidine ethyl ester; (9) *N,O-bis*-PFP-norecgonine ethyl ester;
(10) COO-HFIP-benzoylecgonine; (11) cocaine; (12) cocaethylene; (13) *N*-PFP-norcocaine; (14) *N*-PFP-
norcocaethylene.

the route of administration, acute versus chronic use, and the order and timing of administration that can modify effects.

In summary, the simultaneous administration of cocaine and alcohol implies both a pharmacological interaction at a pharmacodynamic level and a pharmacokinetic interaction. The latter involves an alteration of cocaine kinetics and metabolism and also the biosynthesis of newly active-metabolites, such as cocaethylene. Cocaethylene is metabolized according to the same pathway as cocaine and its detection in biological fluids is indicative of the concomitant consumption of cocaine and alcohol.

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