

Pharmacodynamic Evaluation of the Cardiovascular Effects after the Coadministration of Cocaine and Ethanol

S. Casey Laizure and Robert B. Parker

Department of Clinical Pharmacy, University of Tennessee, Memphis, Tennessee

Received July 30, 2008; accepted November 10, 2008

ABSTRACT:

One of the most common drug dependencies occurring with alcoholism is cocaine dependence. This combination is particularly worrisome because of the increased risk of cardiovascular events associated with their coabuse. Although it is well known that ethanol increases the cardiovascular effects of cocaine by inhibiting cocaine clearance and the formation of cocaethylene, it has also been postulated that ethanol enhances the cardiovascular effects of cocaine independent of the two latter mechanisms. In this study, we investigated the cardiovascular pharmacodynamics of the cocaine-ethanol interaction to determine whether ethanol directly enhanced the cardiovascular effects of cocaine. Dogs ($n = 6$) were administered cocaine alone (3 mg/kg i.v.) and in combination with ethanol (1 g/kg i.v.) on separate study days. Blood pressure, heart rate, and the electrocardiogram were monitored continuously, and blood samples were collected periodically after drug administra-

tion. Concentration-time data were fitted to a two-compartment model, and concentration-effect data were fitted to a simple E_{\max} model using WinNonlin software. Pharmacokinetic and pharmacodynamic parameters were compared between the two treatment phases by a paired t test. The administration of ethanol before cocaine resulted in a decrease in cocaine clearance, but there were no differences in any of the other pharmacokinetic or pharmacodynamic parameter values between the cocaine alone and cocaine plus ethanol phases. As has been demonstrated in previous animal and human studies, the clearance of cocaine was decreased by prior administration of ethanol. However, ethanol did not change the concentration-effect relationship of the cardiovascular response to cocaine administration. It is concluded from this study that ethanol does not directly enhance the cardiovascular effects of cocaine.

It is well accepted that the coabuse of ethanol with cocaine causes an increase in cardiovascular effects and toxicity compared with abuse of cocaine alone (Farré et al., 1993; Schechter and Meehan, 1995; McCance-Katz et al., 1998; Mehta et al., 2002). Various investigators have speculated that the increase in cardiovascular effects when cocaine and ethanol are coadministered is secondary to the formation of the active metabolite, cocaethylene, resulting from the inhibition of the metabolism of cocaine by ethanol and a pharmacodynamic interaction between cocaine and ethanol (Perez-Reyes and Jeffcoat, 1992; McCance-Katz et al., 1993; Schechter and Meehan, 1995; Henning and Wilson, 1996; Farré et al., 1997; Pan and Hedaya, 1999).

The combined administration of cocaine and ethanol results in the formation of cocaethylene, an active metabolite formed by transesterification between cocaine and ethanol. The pharmacological activity of cocaethylene has been studied in animals and was found to be similar to that of cocaine, but cocaethylene has been reported to be more toxic than cocaine with a lower LD_{50} in rats (Hearn et al., 1991). It clearly has the potential to contribute to the increased cardiovascular effects when cocaine and ethanol are coadministered. Ethanol, in addition to resulting in the formation of cocaethylene, also inhibits the clearance of cocaine from the body. The decreased clearance causes a

greater accumulation of cocaine plasma concentrations with repeated administrations such as those occurring during a cocaine binge and an increase in the duration of activity due to the inhibition of metabolism of cocaine.

Thus, there is evidence from previous studies that the formation of cocaethylene and the inhibition of metabolism of cocaine are factors contributing to the increased cardiovascular effects seen after the coadministration of cocaine and ethanol, but there is no evidence available to ascertain the potential pharmacodynamic interaction between cocaine and ethanol, which some investigations have speculated about. The present study was designed to determine whether ethanol administration before cocaine enhanced the effects on the cardiovascular system compared with cocaine given alone. The dog was deemed a good model for the study of a pharmacodynamic interaction between cocaine and ethanol because our previous experience using the cocaine and ethanol doses given in this study did not produce quantifiable plasma concentrations of cocaethylene (Parker et al., 1998). Thus, the combined effects of cocaine and ethanol on the cardiovascular system could be evaluated without being confounded by the formation of the active metabolite, cocaethylene.

Materials and Methods

Animal Model. This protocol was approved by the Animal Care and Use Committee of the University of Tennessee, Memphis. Six, adult, conditioned, mongrel dogs weighting between 17.2 and 20.6 kg underwent a 1-week training program to acclimate them to standing in a nylon sling. After this training period, each dog underwent a surgical procedure under general anesthesia for placement of an arterial indwelling silicone catheter with a subcu-

This work was supported by the National Heart, Lung and Blood Institute National Institutes of Health [Grant R15HL54311].

Article, publication date, and citation information can be found at <http://dmd.aspetjournals.org>.

doi:10.1124/dmd.108.023531.

TABLE 1

Pharmacokinetic and pharmacodynamic parameter estimates

Estimates \pm S.D. from pharmacokinetic analysis, the maximum percentage increase over baseline for heart rate, systolic and diastolic blood pressure, and QRS duration, and the estimates for E_0 , EC_{50} , and E_{max} from six dogs given cocaine alone and cocaine plus ethanol. Only the CI was found to be significantly different between the cocaine alone and cocaine plus ethanol treatment phases.

	Cocaine				Cocaine plus Ethanol			
	Value	E_0	EC_{50}	E_{max}	Value	E_0	EC_{50}	E_{max}
Pharmacokinetics								
k (min^{-1})	0.016 \pm 0.0040				0.0119 \pm 0.0041			
V_{ss} (l/kg)	2.5 \pm 0.61				3.1 \pm 0.97			
Cl (l/min)	1.24 \pm 0.123				0.79 \pm 0.283†			
C_{max} (ng/ml)	2838 \pm 497				2804 \pm 1016			
Maximum effect over baseline (%)								
Heart rate	49 \pm 31				53 \pm 28			
Systolic BP	46 \pm 13				49 \pm 28			
Diastolic BP	88 \pm 44				79 \pm 37			
QRS	18 \pm 10				24 \pm 10			
Simple E_{max}								
Heart rate (beats/min)		93 \pm 16	4482 \pm 5330	188 \pm 62		96 \pm 15	1477 \pm 1239	164 \pm 47
Systolic BP (mm Hg)		152 \pm 22	276 \pm 161	224 \pm 19		148 \pm 23	565 \pm 404	233 \pm 35
Diastolic BP (mm Hg)		94 \pm 15	619 \pm 164	166 \pm 13		94 \pm 10	403 \pm 183	153 \pm 9
QRS (ms)		76 \pm 7	11,797 \pm 6014	128 \pm 32		61 \pm 8	599 \pm 7549	94 \pm 17

BP, blood pressure.

taneous access port (V-A-P Access Port, model 6PV; Access Technologies, Skokie, IL). The dogs were given antibiotics postoperatively to prevent infection and allowed to convalesce for 7 days after surgery. Catheter patency was maintained by daily flushing with heparinized saline (250 units/ml).

Experimental Protocol. On each study day, the dog was put in the sling, and an intravenous catheter was placed in a foreleg vein for drug administration. Blood pressure was monitored continuously by connecting a Gold Statham P23D6 pressure transducer and using an VR-16 multichannel recorder (Electronics for Medicine, Pleasantville, NY) via the arterial access port. Dogs received a 3 mg/kg dose of cocaine as the hydrochloride salt delivered by an infusion pump over approximately 5 min. On study days when both ethanol and cocaine were given, 1 g/kg ethanol was given immediately before the cocaine infusion as a 40-min infusion of an ethanol-saline solution. Each dog received cocaine alone and ethanol before cocaine on separate study days in this repeated-measures design.

Arterial blood samples (4 ml) were collected for the determination of cocaine, benzoylecgonine, and cocaethylene plasma concentrations at 0, 3, 5, 10, 20, 35, 65, 125, 185, and 425 min after the start of the cocaine infusion. Samples were collected into Vacutainer tubes containing 30 mg of sodium fluoride, gently mixed, and put on ice immediately. Within 30 min of sample collection, plasma was separated by centrifugation for 10 min at 2000 rpm and stored on ice until transferred to a -70°C freezer until analysis. Plasma cocaine and cocaethylene concentrations were determined by a high-performance liquid chromatography method developed in our laboratory as described previously (Williams et al., 1996).

Data Analysis. The following general equation was fit to the cocaine plasma concentrations using WinNonlin software (version 4.1; Pharsight, Mountain View, CA):

$$C_t = \sum_{i=1}^n \frac{C_i(1 - e^{-kT})}{T \times \lambda_i} \times e^{-k(t-T)}$$

where C_i is the i th coefficient, λ_i is the i th exponent, n equals the number of coefficient and exponent pairs, t equals the time after the start of the infusion, T is equal to the infusion time, and $t - T$ equals the postinfusion time (when $t \leq T$, $t = T$). Clearance (Cl) was calculated by

$$\text{Cl} = \frac{\text{Dose}}{\sum_{i=1}^n \frac{C_i}{\lambda_i}}$$

volume of distribution at steady state (V_{ss}) was calculated by

$$V_{ss} = \frac{\text{Dose} \times \sum_{i=1}^n \frac{C_i}{\lambda_i^2}}{\sum_{i=1}^n \left(\frac{C_i}{\lambda_i} \right)^2}$$

and half-life ($t_{1/2}$) was calculated by

$$t_{1/2} = \frac{\ln 2}{\lambda_z}$$

where λ_z equals the elimination rate constant of the terminal slope.

The concentration-effect relationship was evaluated by fitting a simple E_{max} model to the concentration-effect plot from 0 to 65 min using the following model equation and a weight of 1.0 (no weight):

$$\text{Effect} = (E_{max} - E_0) \times \left(\frac{C}{C + EC_{50}} \right)$$

where E_0 is the effect at baseline, E_{max} is the maximum effect, EC_{50} is the plasma concentration that achieves one-half the maximum effect, and C is the measured plasma concentration.

The maximum observed effect for heart rate, systolic and diastolic blood pressure, and QRS duration expressed as the percentage increase over baseline and pharmacokinetic and pharmacodynamic model parameter estimates were compared between the 3 mg/kg cocaine and 3 mg/kg cocaine plus 1 g/kg ethanol treatment phases using a paired t test.

Results

The model of best fit to the cocaine plasma concentration-time data was a two-compartment model using a weight factor of $1/y$ (the reciprocal of the predicted concentration). The estimates of the pharmacokinetic parameters are given in Table 1 along with the peak concentrations achieved (C_{max}), the maximum effect of each measured cardiovascular parameter as a percentage relative to baseline, and the mean \pm S.D. for the parameters of the simple E_{max} fits, E_0 (baseline effect), EC_{50} (cocaine plasma concentration at one-half the E_{max}), and E_{max} (the maximum possible effect). There was a significant decrease in the Cl of cocaine when ethanol administration

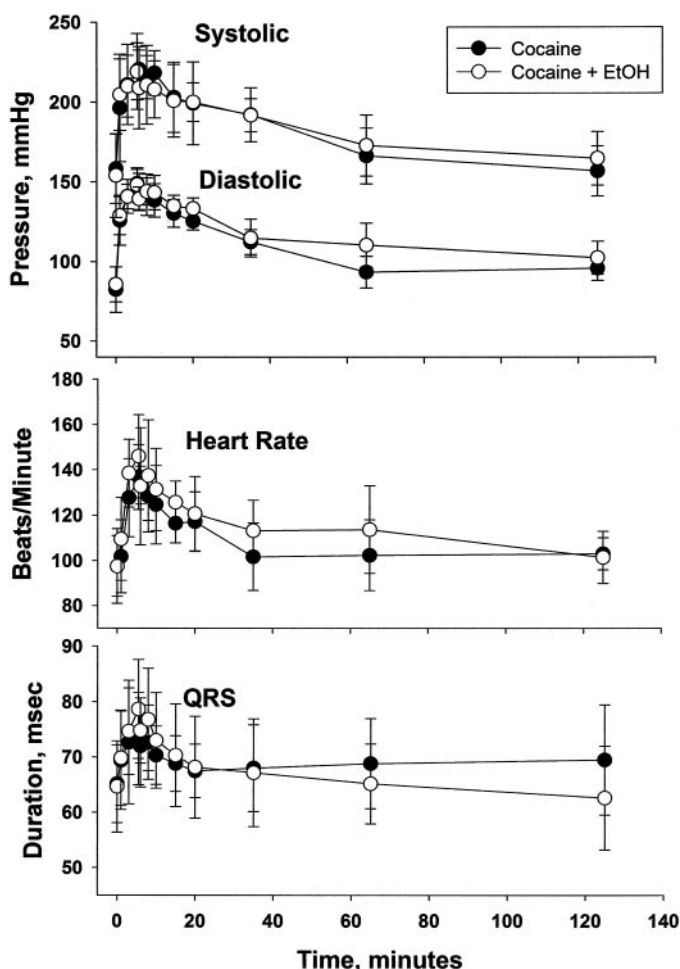


FIG. 1. Plots of blood pressure, heart rate, and QRS duration (mean \pm S.D., $n = 6$) versus time from 0 to 125 min after infusion of 3 mg/kg cocaine given alone and after a 3 mg/kg cocaine infusion preceded by a 1 g/kg ethanol infusion.

preceded the cocaine infusion (1.24 versus 0.79 l/min, $p < 0.05$). The peak effects are similar although there seems to be a slightly greater effect of the cocaine-ethanol combination on blood pressure at the latter time points as seen in Fig. 1. However, no significant differences in the blood pressure effect of cocaine alone and after ethanol administration occurred at any time point. The maximum effect was not altered by the administration of 1 g/kg ethanol before cocaine administration with no differences in the percentage increases in heart rate, systolic blood pressure, diastolic blood pressure, or QRS duration between the two treatment phases (Table 1). The parameter estimates of the simple E_{\max} model also did not differ between treatment phases with essentially superimposable predicted concentration-effect relationships for heart rate and systolic and diastolic blood pressure (Fig. 2).

Discussion

The interaction between cocaine and ethanol results in increased morbidity and mortality due primarily to cardiovascular toxicity (Henning et al., 1994; Rose, 1994; McCance-Katz et al., 1998; Pennings et al., 2002). Three mechanisms have been proposed as potentially contributing to the enhanced cardiovascular toxicity when cocaine and ethanol are coadministered: the inhibition of cocaine elimination by ethanol, the formation of the active metabolite, cocaethylene, in the presence of ethanol, and a pharmacodynamic interaction between cocaine and ethanol (Henning et al., 1994; Henning and Wilson, 1996;

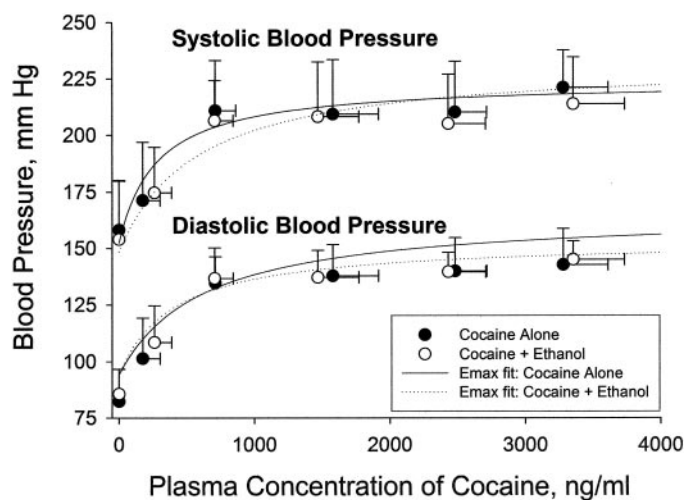


FIG. 2. Concentration-effect plots of blood pressure. Each data point represents the mean concentration-effect with the vertical error bar indicating the S.D. of the measured effect and the horizontal error bar representing the S.D. in the cocaine plasma concentration. The solid and broken lines are derived from the simple E_{\max} model equation using the mean ($n = 6$) values of E_0 , EC_{50} , and E_{\max} for cocaine alone and cocaine plus ethanol. The virtually superimposable E_{\max} fits indicate that ethanol does not alter the concentration-effect relationship of cocaine.

McCance-Katz et al., 1998; Wilson et al., 2001). The metabolism of cocaine to inactive metabolites by carboxylesterases is inhibited by ethanol, causing a decrease in cocaine clearance (Perez-Reyes and Jeffcoat, 1992; Farré et al., 1993; McCance-Katz et al., 1998) and increased exposure to cocaine. Cocaine is an extensively metabolized drug with only 2% of an intravenous dose recovered from the urine as unchanged drug (Ambre et al., 1988). The predominant pathway for elimination of cocaine is by enzymatic hydrolysis with the formation of the inactive metabolites benzoylecgonine and ecgonine methyl ester that undergo renal elimination (Ambre et al., 1984; Ambre, 1985). In most individuals studied, the greatest proportion of the administered dose is eliminated as benzoylecgonine followed by ecgonine methyl ester (Ambre et al., 1988; Cone et al., 1998; Kolbrich et al., 2006).

Ingestion of ethanol before cocaine administration decreases the clearance of cocaine and reduces the formation of benzoylecgonine. The presence of ethanol also results in the formation of the active metabolite, cocaethylene, by transesterification with ethanol (Bourland et al., 1998). Cocaethylene is reported to have similar pharmacological activity on the cardiovascular system and in the central nervous system as cocaine. Direct comparisons of the cardiovascular effects of cocaine and cocaethylene show that it is equipotent to or slightly less potent than cocaine on heart rate, diastolic blood pressure, and systolic blood pressure (Hart et al., 2000; Schindler et al., 2001), and it is a more potent sodium channel blocker in the myocardium than cocaine (Xu et al., 1994). Both formation of cocaethylene and inhibition of cocaine elimination contribute to an increase in the cardiovascular effects when ethanol is coingested with cocaine. A third potential mechanism is direct synergistic activity between cocaine and ethanol on the cardiovascular system (Farré et al., 1993; Henning et al., 1994; McCance-Katz et al., 1998). It is hypothesized that although ethanol has minimal cardiovascular effects when given alone, it might enhance the cardiovascular effects of cocaine by a mechanism separate from the inhibition of cocaine elimination or formation of cocaethylene.

In the present study, the pharmacokinetic and pharmacodynamic interaction between cocaine and ethanol was studied in the dog. This allowed an evaluation of the cocaine-ethanol interaction without the

confounding factor of cocaethylene formation as no quantifiable concentrations of cocaethylene occurred (lower limit of quantification = 25 ng/ml). In a previous study conducted in our laboratory of the pharmacodynamics of cocaethylene in the dog, a 1 mg/kg dose of cocaethylene producing only mild cardiovascular effects resulted in a mean peak concentration ($n = 6$) of 1381 ng/ml (Parker et al., 1998). These previous data demonstrated that a cocaethylene concentration of 25 ng/ml is a subphysiological concentration relative to the cardiovascular effects measured in this study.

There was no evidence of synergistic or additive cardiovascular effects of cocaine-ethanol administration as the concentration-effect relationship was the same when cocaine was given alone and when it was given after the administration of 1 g/kg ethanol. These results suggest that a pharmacodynamic interaction between cocaine and ethanol does not contribute to the increased cardiovascular effects that occur with the coadministration of cocaine and ethanol.

The coingestion of cocaine and ethanol has been studied in both animals and humans. The inhibition of conversion of cocaine to benzoylecgonine with a significant decrease in clearance of cocaine ranging from 10 to 25% has been a consistent finding in several species studied (McCance-Katz et al., 1998; Parker et al., 1998; Pan and Hedaya, 1999; Hart et al., 2000). However, there has been inconsistency in the reported alteration in peak cocaine concentrations and pharmacological effects with the coadministration of cocaine and ethanol. Some studies report an increase in peak cocaine concentrations or effects (Foltin and Fischman, 1989; Perez-Reyes and Jeffcoat, 1992; Farré et al., 1993, 1997; Cami et al., 1998; McCance-Katz et al., 1998), whereas other studies report no significant changes (Uszenski et al., 1992; Henning et al., 1994; Parker et al., 1996; Laizure et al., 2003). The differing results can be reconciled by taking into account the route of cocaine administration used in the studies. Cocaine behaves pharmacokinetically as a high-extraction, hepatically eliminated drug undergoing significant first-pass metabolism, which will result in a significant difference in cocaine disposition depending on the route of administration. Studies in which cocaine is administered by routes subject to first-pass metabolism, i.e., orally by insufflation (snorting) or intraperitoneally, will demonstrate increased cocaine peak concentrations and effects in the presence of ethanol, whereas studies with administration by routes not subject to first-pass metabolism, i.e., inhalation (smoking) or intravenously, will demonstrate no change in the peak cocaine concentration or effect.

The other contributing factor to enhanced cardiovascular effects of the cocaine-ethanol combination is the formation of cocaethylene. After a single intravenous dose of cocaine in humans, approximately 17% of the administered dose is ultimately converted to cocaethylene (Harris et al., 2003). This relatively low rate of formation is consistent with the low cocaethylene concentrations found in patients admitted to emergency rooms exhibiting signs of cocaine toxicity and forensic studies in which the reported cocaethylene concentrations ranged from 0 to 249 ng/ml (Bailey, 1993; Brookoff et al., 1996; Blaho et al., 2000; Harris et al., 2003). The corresponding cocaine concentrations ranged from 26 to 1455 ng/ml. These data, although limited, do not support the contention that the slower elimination of cocaethylene will lead to increased exposure to cocaethylene compared with cocaine with repeated cocaine dosing in the presence of ethanol. This presumption has often been stated on the basis of the longer half-life of cocaethylene. However, the maximum plasma concentrations achieved after repeated dosing is determined by the fraction of cocaine converted to cocaethylene and the clearance of the drug not its volume or half-life. In humans, cocaethylene is reported to have a larger volume of distribution than cocaethylene (2.74 versus 1.94 l/kg), which will result in a longer half-life. The reported mean

clearance values differed by only approximately 20% (Hart et al., 2000). Thus, the accumulation of cocaethylene after the repeated administration of cocaine in the presence of ethanol does not seem to result in high concentrations of cocaethylene because of the relatively small fraction of the cocaine dose converted to cocaethylene and its rapid clearance. This may explain why cocaethylene levels in patients admitted to emergency rooms with cocaine toxicity after cocaine and ethanol ingestion have demonstrated relatively low cocaethylene concentrations even though cocaethylene has a significantly longer half-life than cocaine.

The coabuse of ethanol with cocaine results in an increase in the cardiovascular effects of cocaine on the cardiovascular system by the inhibition of cocaine hydrolysis and the formation of the active metabolite, cocaethylene. In this study of cocaine and ethanol coadministration in the dog, there was no evidence of a pharmacodynamic interaction contributing to the enhanced cardiovascular effects reported when cocaine and ethanol are coadministered.

References

- Ambre J (1985) The urinary excretion of cocaine and metabolites in humans: a kinetic analysis of published data. *J Anal Toxicol* **9**:241–245.
- Ambre J, Fischman M, and Ruo TI (1984) Urinary excretion of ecgonine methyl ester, a major metabolite of cocaine in humans. *J Anal Toxicol* **8**:23–25.
- Ambre J, Ruo TI, Nelson J, and Belknap S (1988) Urinary excretion of cocaine, benzoylecgonine, and ecgonine methyl ester in humans. *J Anal Toxicol* **12**:301–306.
- Bailey DN (1993) Plasma cocaethylene concentrations in patients treated in the emergency room or trauma unit. *Am J Clin Pathol* **99**:123–127.
- Blaho K, Logan B, Winbery S, Park L, and Schwilke E (2000) Blood cocaine and metabolite concentrations, clinical findings, and outcome of patients presenting to an ED. *Am J Emerg Med* **18**:593–598.
- Bourland JA, Martin DK, and Mayersohn M (1998) In vitro transesterification of cocaethylene (ethylcocaine) in the presence of ethanol. esterase-mediated ethyl ester exchange esterase-mediated ethyl ester exchange. *Drug Metab Dispos* **26**:203–206.
- Brookoff D, Rotondo MF, Shaw LM, Campbell EA, and Fields L (1996) Coacetylene levels in patients who test positive for cocaine. *Ann Emerg Med* **27**:316–320.
- Cami J, Farré M, González ML, Segura J, and de la Torre R (1998) Cocaine metabolism in humans after use of alcohol: clinical and research implications. *Recent Dev Alcohol* **14**:437–455.
- Cone EJ, Tsadik A, Oyler J, and Darwin WD (1998) Cocaine metabolism and urinary excretion after different routes of administration. *Ther Drug Monit* **20**:556–560.
- Farré M, de la Torre R, González ML, Terán MT, Roset PN, Menoyo E, and Cami J (1997) Cocaine and alcohol interactions in humans: neuroendocrine effects and cocaethylene metabolism. *J Pharmacol Exp Ther* **283**:164–176.
- Farré M, de la Torre R, Llorente M, Lamas X, Ugena B, Segura J, and Cami J (1993) Alcohol and cocaine interactions in humans. *J Pharmacol Exp Ther* **266**:1364–1373.
- Foltin RW and Fischman MW (1989) Effects of the combination of cocaine and marijuana on the task-elicited physiological response. *NIDA Res Monogr* **95**:359–360.
- Harris DS, Everhart ET, Mendelson J, and Jones RT (2003) The pharmacology of cocaethylene in humans following cocaine and ethanol administration. *Drug Alcohol Depend* **72**:169–182.
- Hart CL, Jatlow P, Sevarino KA, and McCance-Katz EF (2000) Comparison of intravenous cocaethylene and cocaine in humans. *Psychopharmacology (Berl)* **149**:153–162.
- Hearn WL, Rose S, Wagner J, Ciarleglio A, and Mash DC (1991) Cocaethylene is more potent than cocaine in mediating lethality. *Pharmacol Biochem Behav* **39**:531–533.
- Henning RJ and Wilson LD (1996) Cocaethylene is as cardiotoxic as cocaine but is less toxic than cocaine plus ethanol. *Life Sci* **59**:615–627.
- Henning RJ, Wilson LD, and Glauser JM (1994) Cocaine plus ethanol is more cardiotoxic than cocaine or ethanol alone. *Crit Care Med* **22**:1896–1906.
- Kolbrich EA, Barnes AJ, Gorelick DA, Boyd SJ, Cone EJ, and Huestis MA (2006) Major and minor metabolites of cocaine in human plasma following controlled subcutaneous cocaine administration. *J Anal Toxicol* **30**:501–510.
- Laizure SC, Mandrell T, Gades NM, and Parker RB (2003) Cocaethylene metabolism and interaction with cocaine and ethanol: role of carboxylesterases. *Drug Metab Dispos* **31**:16–20.
- McCance-Katz EF, Kosten TR, and Jatlow P (1998) Concurrent use of cocaine and alcohol is more potent and potentially more toxic than use of either alone—a multiple-dose study. *Biol Psychiatry* **44**:250–259.
- McCance-Katz EF, Price LH, McDougle CJ, Kosten TR, Black JE, and Jatlow PI (1993) Concurrent cocaine-ethanol ingestion in humans: pharmacology, physiology, behavior, and the role of cocaethylene. *Psychopharmacology (Berl)* **111**:39–46.
- Mehta MC, Jain AC, and Billie M (2002) Effects of cocaine and alcohol alone and in combination on cardiovascular performance in dogs. *Am J Med Sci* **324**:76–83.
- Pan WJ and Hedaya MA (1999) Cocaine and alcohol interactions in the rat: effect on cocaine pharmacokinetics and pharmacodynamics. *J Pharm Sci* **88**:459–467.
- Parker RB, Laizure SC, Williams CL, Mandrell TD, and Lima JJ (1998) Evaluation of dose-dependent pharmacokinetics of cocaethylene and cocaine in conscious dogs. *Life Sci* **62**:333–342.
- Parker RB, Williams CL, Laizure SC, Mandrell TD, LaBranche GS, and Lima JJ (1996) Effects of ethanol and cocaethylene on cocaine pharmacokinetics in conscious dogs. *Drug Metab Dispos* **24**:850–853.
- Pennings EJ, Leccese AP, and Wolff FA (2002) Effects of concurrent use of alcohol and cocaine. *Addiction* **97**:773–783.
- Perez-Reyes M and Jeffcoat AR (1992) Ethanol/cocaine interaction: cocaine and cocaethylene

- plasma concentrations and their relationship to subjective and cardiovascular effects. *Life Sci* **51**:553–563.
- Rose JS (1994) Cocaethylene: a current understanding of the active metabolite of cocaine and ethanol. *Am J Emerg Med* **12**:489–490.
- Schechter MD and Meehan SM (1995) The lethal effects of ethanol and cocaine and their combination in mice: implications for cocaethylene formation. *Pharmacol Biochem Behav* **52**:245–248.
- Schindler CW, Zheng JW, and Goldberg SR (2001) Effects of cocaine and cocaine metabolites on cardiovascular function in squirrel monkeys. *Eur J Pharmacol* **431**:53–59.
- Uszenski RT, Gillis RA, Schaer GL, Analouei AR, and Kuhn FE (1992) Additive myocardial depressant effects of cocaine and ethanol. *Am Heart J* **124**:1276–1283.
- Williams CL, Laizure SC, Parker RB, and Lima JJ (1996) Quantitation of cocaine and cocaethylene in canine serum by high-performance liquid chromatography. *J Chromatogr B Biomed Appl* **681**:271–276.
- Wilson LD, Jeromin J, Garvey L, and Dorbandt A (2001) Cocaine, ethanol, and cocaethylene cardiotoxicity in an animal model of cocaine and ethanol abuse. *Acad Emerg Med* **8**:211–222.
- Xu YQ, Crumb WJ Jr, and Clarkson CW (1994) Cocaethylene, a metabolite of cocaine and ethanol, is a potent blocker of cardiac sodium channels. *J Pharmacol Exp Ther* **271**:319–325.

Address correspondence to: Dr. S. Casey Laizure, Department of Clinical Pharmacy, University of Tennessee, Suite 308, 910 Madison Ave., Memphis, TN 38163. E-mail: claizure@utmem.edu
