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The Effect of Ethanol on Oral Cocaine Pharmacokinetics Reveals an Unrecognized
Class of Ethanol-Mediated Drug Interactions

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Running Title

Ethanol inhibition of carboxylesterase hydrolysis

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Document Statistics

Number of text pages: 23

Number of tables: 2

Number of Figures: 3

Number of References: 44

Number of Words

Abstract: 248

Introduction: 475

Discussion: 1862

Abbreviations

BE = benzoylecgonine

EME= ecgonine methyl ester

CES1 = carboxylesterase 1

CES2 = carboxylesterase 2

EtOH = ethanol

CE = cocaethylene

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Abstract

Ethanol decreases the clearance of cocaine by inhibiting the hydrolysis of cocaine to benzoylecgonine and ecgonine methyl ester by carboxylesterases, and there is a large body of literature describing this interaction as it relates to the abuse of cocaine. In this study, we describe the effect of intravenous ethanol on the pharmacokinetics of cocaine after intravenous and oral administration in the dog. The intent is to determine the effect ethanol has on metabolic hydrolysis using cocaine metabolism as a surrogate marker of carboxylesterase activity. Five dogs were administered intravenous cocaine alone, intravenous cocaine after ethanol, oral cocaine alone, and oral cocaine after ethanol on separate study days. Cocaine, benzoylecgonine, and cocaethylene concentrations were determined by HPLC. Cocaine had poor systemic bioavailability with an AUC approximately fourfold higher after intravenous compared to oral administration. The co-administration of ethanol and cocaine resulted in a 23% decrease in the clearance of intravenous cocaine and a 300% increase in the bioavailability of oral cocaine. Cocaine behaves as a high extraction drug, which undergoes first-pass metabolism in the intestines and liver that is profoundly inhibited by ethanol. We infer from these results that ethanol could inhibit the hydrolysis of other drug compounds subject to hydrolysis by carboxylesterases. Indeed, there are numerous commonly prescribed drugs with significant carboxylesterase-mediated metabolism such as enalapril, lovastatin, irinotecan, clopidogrel, prasugrel, methylphenidate, meperidine, and oseltamivir that may interact with ethanol. The clinical significance of ethanol's interaction with specific drugs subject to carboxylesterase hydrolysis is not well recognized and has not been adequately studied.

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INTRODUCTION

Mammalian carboxylesterases are α,β -hydrolase-fold proteins that catalyze the hydrolysis of a vast array of endogenous and exogenous esters, amides, thioesters, and carbamates (Sato and Hosokawa 2006). Two carboxylesterases have been identified, carboxylesterase 1 (CES1) and carboxylesterase 2 (CES2) that are primary metabolic pathways of drugs subject to catalytic hydrolysis in humans (Sato and Hosokawa 1998; Schwer et al. 1997). The most common type of drug subject to hydrolysis in humans is an ester prodrug specifically developed to be rapidly hydrolyzed to an active metabolite after absorption from the gastrointestinal tract (Sato and Hosokawa 2006), but there are also drugs in which catalytic hydrolysis by carboxylesterases plays an important role in the conversion of an active drug to inactive metabolite (Farid et al. 2008; Patrick et al. 2007; Tang et al. 2006; Zhang et al. 1999). Therefore, alterations in the catalytic activity of these enzymes could play a key role in both the disposition and pharmacological actions of substrate drugs. Unlike drug-drug interactions involving the inhibition of the metabolism of agents that are substrates for the cytochrome P450 enzymes, the consequences of interactions involving inhibition of carboxylesterases have generally not been explored. The potential clinical significance of alterations in carboxylesterase activity could be important as many drugs from numerous therapeutic classes including angiotensin converting enzyme inhibitors, anticancer agents, opiate analgesics, HMG-CoA inhibitors, central nervous system stimulants, neuramidase inhibitors, and antiplatelet drugs are substrates.

The most extensively studied drug interaction with carboxylesterases is the interaction between cocaine and ethanol. As shown in Figure 1, cocaine is eliminated primarily by hydrolysis to benzoylecgonine (BE) and ecgonine methyl ester (EME) by CES1 and CES2 (Brzezinski et al. 1994; Dean et al. 1991; Laizure et al. 2003; Pindel et al. 1997). Ethanol has been demonstrated in vitro to inhibit both carboxylesterases (Roberts et al. 1993), and in animals and humans to inhibit the hydrolysis of cocaine to BE by CES1 (Dean et al. 1992; Henning et al. 1994; McCance-Katz et al. 1993). However, the primary focus of previous studies has been characterizing the pharmacokinetic and pharmacodynamic interaction as it relates to the abuse of cocaine and ethanol, thus cocaine was usually administered by non-oral routes (IV, intraperitoneal, smoking,

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insufflation). Cocaine, which is a high extraction drug, should demonstrate route-dependent disposition and would therefore be an excellent model substrate for the effect of ethanol on carboxylesterase-mediated hydrolysis of orally administered drugs. Since many of the therapeutic agents that are carboxylesterase substrates also undergo high first-pass, carboxylesterase-dependent metabolism, the effects of ethanol on cocaine's oral disposition would give important insight into the magnitude and extent of drug interactions between ethanol and other drugs that undergo first-pass metabolism by these enzymes. Therefore, the objective of the present study was to use oral cocaine as a marker compound to determine the effect of ethanol-mediated inhibition of CES1 and CES2 on orally administered drugs.

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METHODS

Animal Model. This study was conducted in five adult, male, conditioned, mongrel dogs (weight 16-21 kg) that were part of an overall evaluation of the effects of ethanol on the pharmacokinetics and cardiovascular pharmacodynamics of cocaine. The animals underwent a 1-week training period in which they were acclimated to the laboratory and trained to stand in a nylon sling. After the training period, each animal received acepromazine (0.1 mg/kg im) and atropine (0.05 mg/kg im) prior to induction of anesthesia with thiopental (25 mg/kg IV). After anesthesia was induced, a cuffed endotracheal tube was placed and anesthesia maintained with 1.5% isoflurane and oxygen. Indwelling silicone catheters (V-A-P Access Port Model 6PV, Access Technologies, Skokie, IL) were implanted into the carotid artery and internal jugular vein of each animal. The catheters were tunneled subcutaneously to the back of the animal's neck and connected to a V-A-P Access Port that was sutured in place underneath the skin. The dogs received pre- and post-operative antibiotics and were allowed to recover for seven days before studies were initiated. During the surgical recovery period, the training to stand in the nylon sling was continued. The catheters were flushed daily with heparinized saline (250 U/ml) to maintain patency. This study was approved by the University of Tennessee Animal Care and Use Committee and was performed according to the *Guide for the Care and Use of Laboratory Animals*.

Experimental Procedures. After an overnight fast prior to each study day, the animals were brought to the laboratory and placed in the nylon sling. All dogs received each of the following treatments on separate study days with each treatment separated by at least 48 hours: 1) 3 mg/kg IV cocaine; 2) 1 gm/kg IV ethanol followed by 3 mg/kg IV cocaine; 3) 4 mg/kg cocaine administered orally in a gelatin capsule; 4) 1 gm/kg IV ethanol followed by 4 mg/kg oral cocaine. All cocaine doses are expressed in mg base equivalents and given in the form of the hydrochloride salt (Sigma-Aldrich, St. Louis, MO). The IV cocaine dose was prepared in sterile 0.9% sodium chloride solution immediately prior to administration and infused into the jugular vein catheter over five minutes by a syringe pump (Harvard Apparatus, Natick, MA). The ethanol solution was prepared by adding absolute ethanol (McCormick Distilling Co., Weston, MO) to sterile 0.9% sodium chloride solution to give a 25% (v/v) solution that was administered over

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40 minutes via the jugular vein catheter. We have previously demonstrated in the dog that this ethanol dose results in moderate intoxication with a mean peak concentration of 144 ± 28 mg/dl (Parker et al. 1996). Arterial blood pressure was continuously monitored using the arterial catheter connected to a Gould Statham P23Db pressure transducer via fluid filled tubing. Blood pressure and lead II of the surface ECG were monitored and recorded using a BioPac Systems 100A recording system (Santa Barbara, CA).

Blood samples (4 ml) were collected through the arterial catheter before and at 3, 5, 7, 10, 15, 20, 25, 35, 65, 125, 185, 365 minutes and 24 hours after the start of the infusion. During the oral cocaine treatments, blood samples were collected before and at 10, 20, 30, 45, 60, 90, 120, 180, 360 minutes, and 24 hours after oral cocaine administration. Blood samples were placed into chilled Vacutainer® (Franklin Lakes, NJ) tubes containing 30 mg of sodium fluoride. Each sample was mixed gently and placed on ice immediately. Within one hour of blood collection, plasma was separated by centrifugation for 10 minutes at 2000 rpm and stored at -70°C until analysis.

Plasma concentrations of cocaine, BE, and cocaethylene were determined by modification of our previously described HPLC assay (Williams et al. 1996). The compounds of interest were extracted from plasma using 130 mg (3 ml) Bond Elut® Certify solid-phase extraction columns (Varian Inc., Palo Alto, CA). The columns were conditioned with methanol and KH_2PO_4 buffer, pH 6.0. Each plasma sample containing 100 ng of the internal standard (lidocaine) was decanted onto the solid-phase extraction column and the columns were then washed with deionized water and 100 mM HCl. The compounds were eluted with 2 ml of methanol/ NH_4OH (98:2), dried under nitrogen at 35°C , and reconstituted in 200 μl of mobile phase. A 170 μl aliquot was then injected onto a LC-ABZ (4.6×250 mm) analytical column (Supelco, Bellefont, PA) with a mobile phase of 50 mM KH_2PO_4 buffer, pH 5.5, and acetonitrile (84:16 v/v) at a flow rate of 1.4 ml/min with detection by UV absorbance at 230 nm.

Data Analysis. Cocaine and BE pharmacokinetic parameters were calculated by standard noncompartmental methods using WinNonlin 3.1 (PharSight Corporation,

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Mountain View, CA). Peak plasma concentrations (C_{\max}) were determined by direct inspection of each animal's plasma concentration-time curves. Cocaine and BE area under the plasma concentration-time curves from time 0-infinity ($AUC_{0-\infty}$) were calculated using the log-linear trapezoidal rule. Elimination rate constant (k_{el}) was estimated by log-linear regression of the terminal portion of the plasma concentration-time curve and elimination half-life ($t_{1/2}$) calculated as $0.693/k_{el}$. Cocaine bioavailability (F) was calculated as $(AUC_{oral} \times Dose_{iv}) / (AUC_{iv} \times Dose_{oral})$. A repeated-measures analysis of variance followed by Dunnett's post-hoc test was used to compare the cocaine and BE pharmacokinetic parameters obtained with the oral cocaine dose to those found with oral cocaine + ethanol and IV cocaine treatments. A p value < 0.05 was considered statistically significant.

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RESULTS

Cocaine and BE pharmacokinetic parameters are summarized in Table 1. Cocaine and corresponding BE concentration-time profiles after administration of oral and IV cocaine are shown in Figure 2. The cocaine $AUC_{0-\infty}$ was approximately 5.5-fold higher after IV compared to oral administration. There was no significant difference in the cocaine terminal elimination half-life noted between the two routes of administration. The systemic bioavailability of cocaine was 0.18 ± 0.05 . The BE $AUC_{0-\infty}$ was two-fold higher after IV versus oral administration.

The cocaine and BE plasma concentration-time profiles after oral administration of cocaine with and without ethanol are shown in Figure 3. Ethanol co-administration produced a four-fold increase in cocaine $AUC_{0-\infty}$. Oral cocaine systemic bioavailability and C_{max} were significantly increased by fourfold and threefold, respectively after ethanol administration. Ethanol pre-treatment did not affect oral cocaine elimination half-life. The BE $AUC_{0-\infty}$ was approximately 2.5-fold higher with ethanol co-administration compared to oral cocaine given alone. Cocaethylene was not detected after the co-administration of ethanol and intravenous cocaine (lower limit of detection was 25 ng/ml), but when ethanol was co-administered with oral cocaine, the mean peak cocaethylene concentration was 30.9 ± 7.3 ng/ml. A significant 33% increase in the IV cocaine $AUC_{0-\infty}$ was seen with the co-administration of ethanol. Ethanol did not significantly affect the BE $AUC_{0-\infty}$ for IV cocaine.

The metabolite to parent AUC ratios (BE/cocaine) for the four treatment phases are shown in Table 1. For oral compared to IV cocaine, the AUC ratio was significantly increased by 2.8 fold. Compared to oral cocaine administered alone, ethanol co-administration reduced the AUC ratio by 40%. Ethanol did not significantly affect the AUC ratios for IV cocaine.

DISCUSSION

Cocaine is a carboxylesterase substrate predominantly eliminated by hydrolysis to BE and EME (Figure 1) by CES1 and CES2 (Cone et al. 1998; Dean et al. 1995; Isenschmid et al. 1992; Kamendulis et al. 1996), and it is one of the few carboxylesterase substrates whose interaction with ethanol has been extensively studied. Studies of the effect of ethanol on cocaine pharmacokinetics have focused on the pharmacodynamic interaction in drug abuse and have administered cocaine by the intravenous, intraperitoneal, nasal, and smoking routes (Cami et al. 1998; Farre et al. 1993; Laizure et al. 2003). All of these routes of administration bypass completely (intravenous and smoking) or partially (intraperitoneal and intranasal) the first-pass metabolism of cocaine. These studies, performed in both humans and animal models, consistently demonstrate that the co-administration of ethanol inhibits the metabolism of cocaine given by non-oral (IV, smoking, intraperitoneal, intranasal) routes resulting in an approximate 20% to 50% decrease in the clearance of cocaine (Farre et al. 1993; Pan and Hedaya 1999; Parker et al. 1996). However, cocaine is a high extraction drug whose elimination following intravenous administration is dependent on liver blood flow, but if given orally cocaine's elimination will be dependent on the fraction unbound in the plasma and the intrinsic clearance. Thus, the magnitude of the ethanol-mediated effect on carboxylesterase substrate disposition would be expected to be much greater after oral administration. The large first-pass metabolism of cocaine is similar to other drugs that are substrates of carboxylesterases making cocaine an excellent probe drug for evaluating the effect of ethanol on orally administered carboxylesterase substrates. The large increase in cocaine's oral bioavailability (F increased from 0.18 to 0.72) demonstrates the potent inhibitory effect of ethanol on catalytic hydrolysis and implicates ethanol in a broad class of drug interactions encompassing numerous important therapeutic agents that have carboxylesterase-dependent metabolism.

The hydrolysis of cocaine predominantly to BE and EME has been reported in rats, pigs, monkeys, and humans (Cone et al. 1998; Evans and Foltin 2004; Kambam et al. 1992; Mets et al. 1999; Saady et al. 1995). When cocaine is given by the intravenous or intraperitoneal route, BE is the most abundant metabolite formed followed by EME. This general finding in multiple species of higher BE metabolite levels after intravenous

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administration of cocaine is evidence of the interspecies consistency of CES1 distribution in the liver and CES2 distribution in the small intestine (Redinbo et al. 2003). Taketani et. al. conducted the most extensive study of interspecies distribution of CES1 and CES2. They reported that CES1 was mainly found in liver tissue with varying amounts of CES2 in different species, and that intestinal tissue contained almost exclusively CES2 in all species tested except the dog. Interestingly, they found no carboxylesterase activity (either CES1 or CES2) in the intestine of the dog and no evidence of carboxylesterase proteins from the gel electrophoresis (Taketani et al. 2007). However, the findings of Taketani et. al. have not been replicated and are not consistent with another recent study in the dog, in which prasugrel, a CES2 substrate (Williams et al. 2008), was shown to be rapidly converted to its corresponding thiolactone metabolite in the dog intestine (Hagihara et al. 2009).

Our data and several additional lines of evidence support the potential role of CES2-mediated gut metabolism of carboxylesterase substrate drugs. First, if first-pass metabolism of oral cocaine by CES1 to BE occurs primarily in the liver, then the fraction of the dose converted to BE should be independent of the route of administration. In other words, as shown with other high extraction drugs such as morphine and propranolol, the dose-normalized AUCs for metabolites formed should be the same for both oral and IV routes of administration (Walle et al., 1979; Osborne et al., 1990). In contrast, we found that the dose-adjusted BE AUC was twofold higher for IV compared to oral cocaine, consistent with intestinal metabolism by an additional pathway. These data, in conjunction with the high levels of CES2 expression in the intestine, suggests that CES2-mediated metabolism in the gut plays an important role in the pre-systemic metabolism of cocaine (Schwer et al., 1997; Satoh et al., 2002; Zhang et al., 2002). Second, there are substantial differences in cocaine bioavailability when it is given by the oral compared to the intraperitoneal route. In rats, cocaine bioavailability ranges from 0.03-0.05 and 0.55-0.65 for oral and intraperitoneal administration, respectively (Ma et al., 1999; Pan and Hedaya, 1999b; Pan and Hedaya, 1999a; Sun and Lau, 2001). Since both intraperitoneal and oral doses undergo hepatic first-pass metabolism, the bioavailabilities should be similar if the liver is the only site of metabolism.

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Therefore, the marked difference in bioavailability between these two routes of administration further suggests that cocaine undergoes intestinal metabolism.

These data indicate that generalizing the effect of ethanol on cocaine metabolism in the dog to humans is a reasonable supposition. In addition, human studies of the interaction between intravenously administered cocaine and ethanol are plentiful and indicate that the clearance of cocaine is inhibited to a similar degree in both dogs and humans after co-administration with ethanol (Farre et al. 1993; Harris et al. 2003; Laizure et al. 2003; Roberts et al. 1993). Additional evidence that ethanol inhibits carboxylesterase hydrolysis in humans is reported for methylphenidate. Methylphenidate undergoes high first-pass metabolism by CES1 to the inactive metabolite, ritalinic acid. The co-administration of ethanol caused a 27% increase in the AUC and a 41% increase in the C_{max} of orally administered methylphenidate in human volunteers (Patrick et al. 2007). This is further evidence that ethanol's inhibition of carboxylesterases demonstrated in our study is applicable to humans and to other drugs that are carboxylesterase substrates. It is interesting to note that the change in bioavailability of methylphenidate is much less than the change in cocaine's bioavailability that we observed in the dog. Despite the well conserved nature of carboxylesterase activity in mammals there are significant interspecies differences in both the distribution and activity of specific carboxylesterase enzymes (Sato and Hosokawa 1995; Song et al. 1999; Takahashi et al. 2009). Another factor could be that while methylphenidate is a CES1 substrate, cocaine is both a CES1 and CES2 substrate, and our data suggests ethanol is an inhibitor of both carboxylesterases. If ethanol is a potent CES2 inhibitor, this could explain the greater effect of ethanol co-administration on cocaine versus methylphenidate bioavailability.

As noted by Patrick et.al. in their human study of the interaction between ethanol and methylphenidate, the inhibition of carboxylesterase hydrolysis by ethanol could be due to the direct inhibition of carboxylesterase activity by ethanol or due to competitive inhibition with the ethylated metabolite formed by transesterification (Patrick et al. 2007). This is an important consideration as it has been previously demonstrated that cocaethylene inhibits the elimination of cocaine (Parker et al. 1996). However, the

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concentrations required to achieve a 25% reduction in cocaine clearance were over 100-fold higher (3796 ± 857 vs. 30.9 ± 7.3 ng/ml) than the cocaethylene C_{max} that occurred in this study (Parker et al. 1998; Parker et al. 1996). This strongly suggests that the cocaethylene concentrations achieved in the present study are nonpharmacologic and that inhibition of cocaine's hydrolysis is due to the direct inhibition of carboxylesterase activity by ethanol.

Our findings identify a new class of drug-drug interactions – ethanol-mediated inhibition of carboxylesterase hydrolysis, which may significantly affect the disposition of a number of widely prescribed drugs that are esters. Most of the ester drugs on the market are inactive prodrugs that are designed to be rapidly metabolized by carboxylesterases, and like cocaine, are high extraction drugs with a large first-pass metabolism. Therefore, ethanol, by inhibiting carboxylesterases, would reduce the formation rate of the active moiety. In this case, ethanol would be expected to markedly reduce the systemic exposure of the active compound and attenuate the therapeutic effects. An important example would be oseltamivir phosphate, which is an inactive ester prodrug that was specifically developed to overcome the poor oral bioavailability of oseltamivir carboxylate (the active neuramidase inhibitor). Oseltamivir phosphate is rapidly absorbed and converted to oseltamivir carboxylate by CES1 (He et al. 1999). The exception to this rapid conversion is in rare individuals who are poor converters (Zhu and Markowitz 2009). Rare genetic variants have been documented that result in low carboxylesterase activity, and this has led to concerns that individuals with variant alleles will not achieve therapeutic effects due to their inability to hydrolyze the prodrug to its active form. It is quite possible given ethanol's potent inhibitory effect on hydrolysis that it could result in poor conversion rates similar to what is seen with variant alleles. Such a drug interaction would be expected to decrease the efficacy of oseltamivir against influenza viruses including the H1N1 strain, and it would be a far more frequent occurrence than the incidence of variant alleles. With over 100 million people in the United States using ethanol (SAMHSA 2004) and the common use of ethanol as a vehicle in cold medications the potential health implications of the interaction between ethanol and oseltamivir are significant on both an individual and societal basis.

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Another widely prescribed drug class that potentially interacts with ethanol would be the thienopyridine antiplatelet drugs, clopidogrel and prasugrel. Clopidogrel is metabolized by the cytochrome P450 system to the intermediate inactive thiolactone metabolite and then to the active metabolite. Both clopidogrel and the intermediate thiolactone are subject to hydrolysis by CES1, a competing pathway, resulting in inactive metabolites. Ethanol by inhibiting hydrolysis by CES1 would be expected to increase the formation of the active metabolite by the cytochrome P450 system increasing the antiplatelet effect of clopidogrel. In contrast, prasugrel is converted to its thiolactone metabolite by CES2 in the intestines, and the thiolactone metabolite is converted to the active metabolite by the cytochrome P450 system. Ethanol would decrease the formation of the thiolactone metabolite increasing the bioavailability of prasugrel. The absorbed prasugrel would no longer have access to CES2, which is primarily localized in the small intestine, so lower levels of the thiolactone metabolite would be available for conversion to the active metabolite. Ethanol would be expected to decrease the antiplatelet effect when co-administered with prasugrel.

The clinical effect of the interaction of ethanol with specific drugs can be postulated based on a knowledge of the drug's metabolic pathway and pharmacodynamics, but ultimately human studies are required before this information can be used to guide therapy in patients. The list of drugs in Table 2 identifies a number of widely prescribed therapeutic agents that are known substrates of carboxylesterases (Farid et al. 2007; Patrick et al. 2007; Pindel et al. 1997; Quinney et al. 2005; Satoh and Hosokawa 2006; Slatter et al. 1997; Tang et al. 2006; Williams et al. 2008; Yang et al. 2009; Zhang et al. 1999), and gives a perspective on the potential broad clinical implications of this interaction. The potential of ethanol to interact with commonly prescribed drugs by inhibition of hydrolysis has not been considered; however, the potent ethanol-mediated inhibition of carboxylesterase hydrolysis demonstrated in the present study identifies a need for clinical studies with specific drugs to establish a better understanding of the carboxylesterase-ethanol interaction and the therapeutic implications.

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Footnotes

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

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FIGURE LEGENDS

Figure 1

The Hydrolysis of Cocaine by CES1 and CES2

Figure 2

Cocaine and Benzoylecgonine Concentration-Time Profiles (mean \pm SEM) after Intravenous and Oral Administration of Cocaine

Figure 3

Cocaine and Benzoylecgonine Concentration-Time Profiles (mean \pm SEM) after the Oral Administration of Cocaine with and without Ethanol

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Table 1

Cocaine and Benzoylecgonine Pharmacokinetic Parameters: Cocaine and benzoylecgonine AUC values determined after IV cocaine administration are normalized to a cocaine dose of 4 mg/kg. The clearance (Cl) values for cocaine given orally represent the oral clearance equivalent to Cl/F. Data expressed as mean \pm SD.

	Oral Cocaine	Oral Cocaine + EtOH	IV Cocaine	IV Cocaine + EtOH
AUC_{0→∞} (mg•min/l)	15.0 \pm 4.7*†	58.6 \pm 10.0	83.1 \pm 15.4†	110.3 \pm 22.5
Cl (l/min)	5.64 \pm 1.84*†	1.38 \pm 0.35	0.96 \pm 0.19†	0.74 \pm 0.20
C_{max} (ng/ml)	116 \pm 98*†	331 \pm 131	2677 \pm 299	2885 \pm 702
T_{max} (min)	83.6 \pm 46.1	99.8 \pm 32.5	-----	-----
t_{1/2} (min)	85.2 \pm 6.6	84.2 \pm 9.1	74.9 \pm 16.7†	84.4 \pm 8.2
F	0.18 \pm 0.05†	0.72 \pm 0.17	-----	-----
CE C_{max} (ng/ml)	ND	30.9 \pm 7.3	ND	ND
BE AUC_{0→∞} (mg•min/l)	172 \pm 46*†	410 \pm 82	357 \pm 22	407 \pm 110
BE/Cocaine AUC_{0→∞}	11.9 \pm 3.0*†	7.1 \pm 1.5	4.2 \pm 0.7	3.7 \pm 0.6

ND: none detected

* p<0.05 compared to IV cocaine

† p<0.05 compared to corresponding EtOH group given by the same route

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Table 2: Common drugs that undergo hydrolysis by carboxylesterases

	CES1	CES2
Hydrolysis to	oseltamivir	prasugrel †
Active Metabolite	benazapril	irinotecan
	quinapril	lovastatin
	imidapril	simvastatin
Hydrolysis to	clopidogrel	cocaine
Inactive Metabolite	methylphenidate	aspirin
	meperidine	

† Prasugrel is hydrolyzed to an inactive metabolite that is the precursor of the active moiety

Figure 1

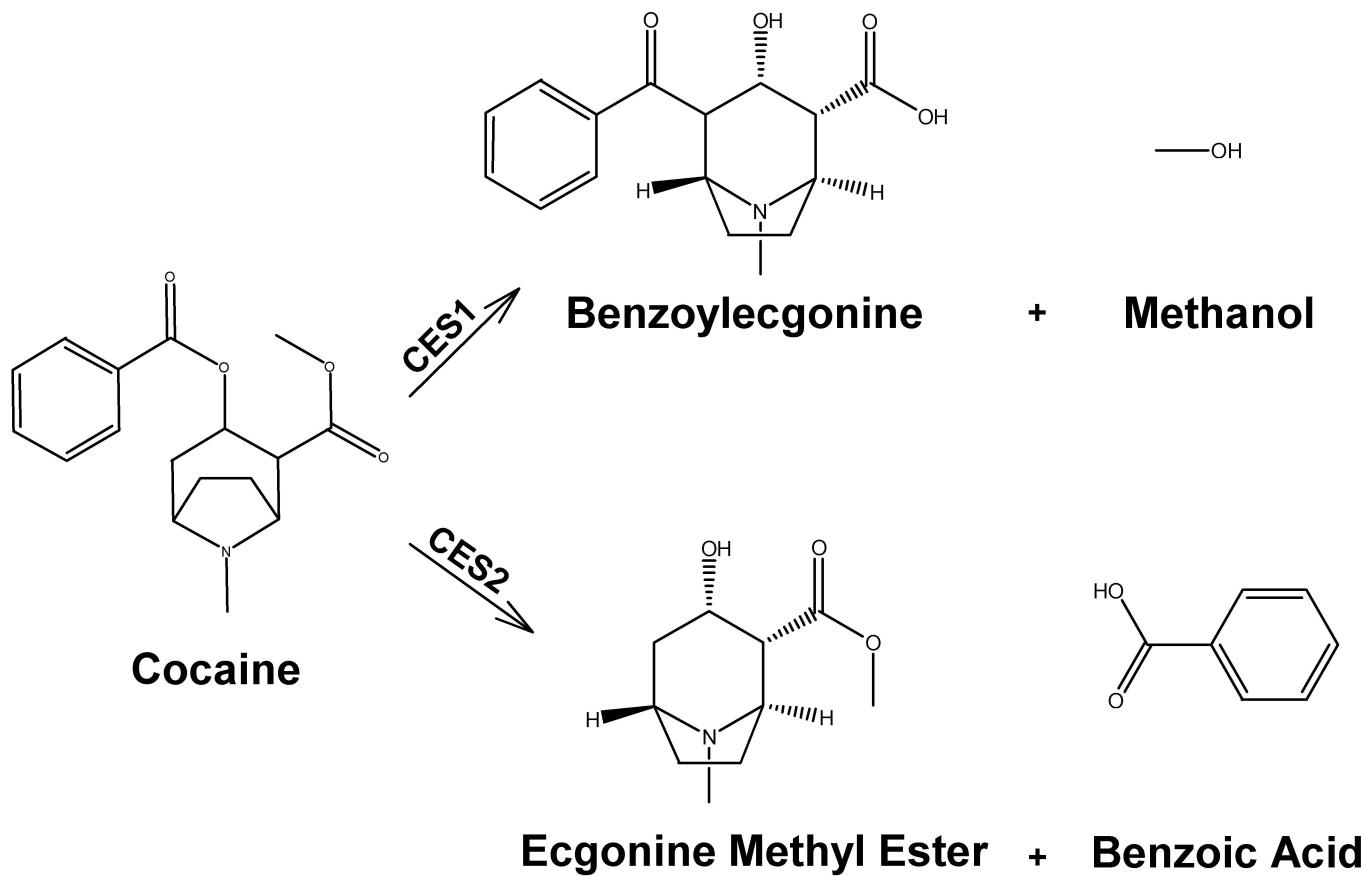


Figure 2

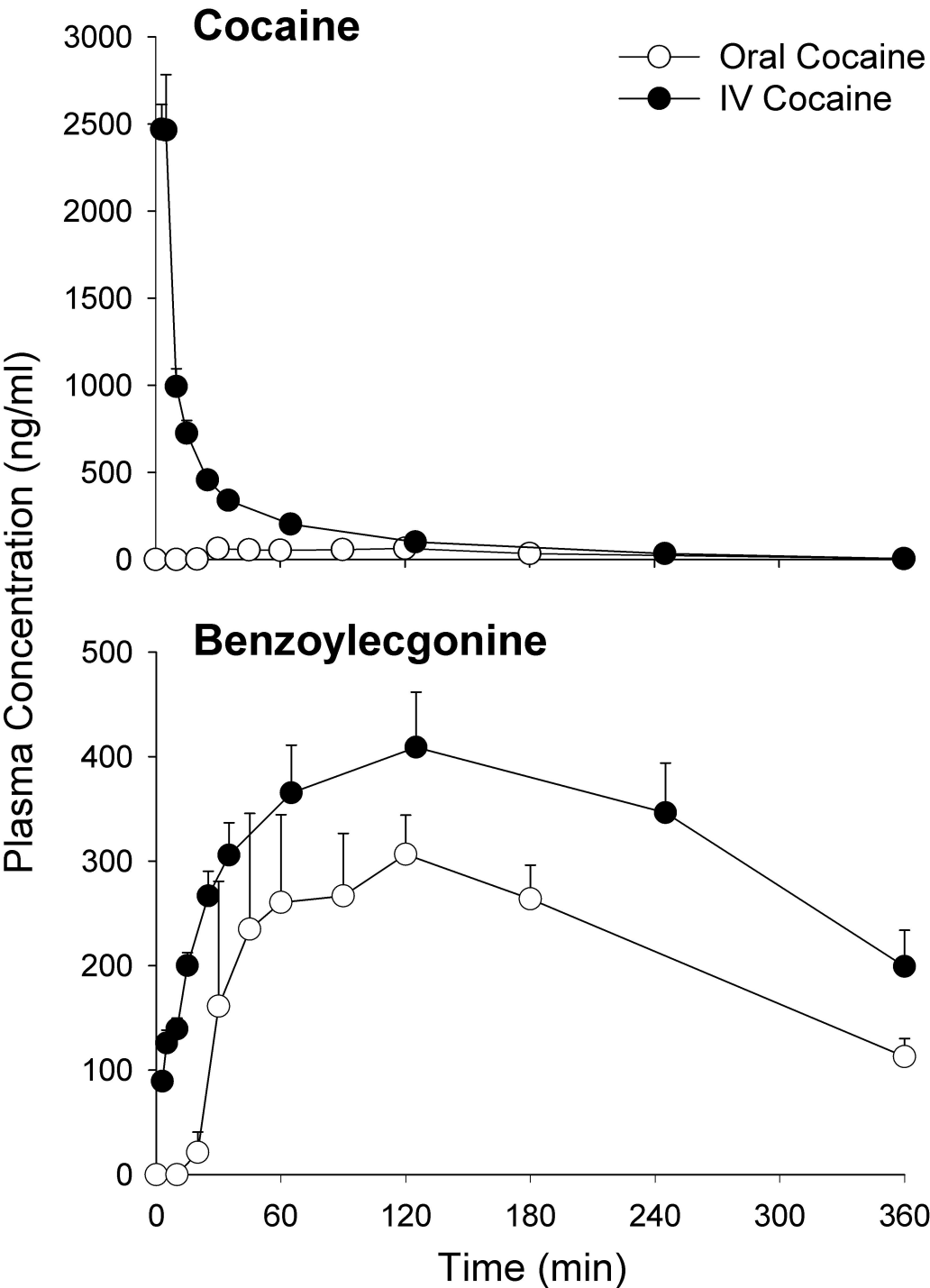


Figure 3

