Cocaine and Alcohol Interactions in the Rat: Effect on Cocaine Pharmacokinetics and Pharmacodynamics

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Received July 13, 1998. Final revised manuscript received October 22, 1998.
Accepted for publication January 20, 1999.

Abstract □ The effect of alcohol coadministration on cocaine pharmacokinetics and pharmacodynamics was investigated in awake, freely moving rats. Cocaine plasma and brain extracellular fluid (ECF) concentration–time profiles were characterized after intraperitoneal (ip) administration of 30 mg/kg cocaine to rats that were pretreated with either normal saline or alcohol at 5 g/kg in a balanced crossover experimental design. The neurochemical response to cocaine administration, measured as the change in dopamine concentration in the nucleus accumbens (N ACC) and the change in the mean arterial blood pressure were monitored simultaneously. Intragastric alcohol administration significantly increased cocaine systemic bioavailability after ip administration from 0.550 ± 0.044 to 0.754 ± 0.071. Also, the absorption rate constant increased from 0.199 ± 0.045 to 0.276 ± 0.059 min^{-1} due to alcohol coadministration; however, this increase was not significant. Alcohol inhibition of cocaine metabolism caused an increase in cocaine elimination half-life from 26.3 ± 3.6 to 40.0 ± 8.1 min. Also, cocaine tissue distribution was enhanced by alcohol, resulting in a significant increase in cocaine volume of distribution. Analysis of the brain cocaine concentration–neurochemical effect relationship by the sigmoid-E_{max} pharmacodynamic model showed that E_{max} increased from 850 ± 200 to 1550 ± 640% of baseline due to alcohol coadministration, whereas EC_{50} decreased from 3400 ± 580 to 2000 ± 650 ng/mL, indicating higher cocaine potency in the presence of alcohol. The estimates of the indirect inhibitory pharmacodynamic model used to examine the plasma cocaine concentration–change in blood pressure relationship were not significantly different after the two treatments. These results indicate that alcohol significantly alters cocaine absorption, distribution, and elimination, resulting in higher and prolonged cocaine plasma concentration. Alcohol coadministration also potentiates the neurochemical response to cocaine administration.

Introduction

The pharmacological activities of cocaine include central nervous system (CNS), cardiovascular, and local anesthetic effects.[1] Cocaine inhibits catecholamine reuptake in the brain, leading to higher catecholamine concentration and producing cocaine stimulant effects.[2] Cocaine can also inhibit peripheral catecholamine reuptake leading to higher peripheral catecholamine concentrations that are primarily responsible for cocaine sympathomimetic effects.[3] It is also believed that cocaine may produce its sympathomimetic effect by a central mechanism.[4] The local anesthetic effect of cocaine results from blocking the sodium channel in sensory neurons, a mechanism that can affect the cardiac action potential leading to slower heart rate and slower cardiac conduction at high cocaine concentrations.[5] The sympathomimetic and the local anesthetic effects of cocaine can lead to opposite effects on the cardiovascular functions, which is responsible for the large variability in the cardiovascular effects of cocaine.[6,7]

Concurrent cocaine and alcohol use is one of the most frequently abused drug combinations.[8] The popularity of this drug combination arises primarily from the fact that abusers of this drug combination experience more intense and longer lasting euphoric effects, while the unpleasant disphoria experienced with cessation of cocaine use is reduced.[9] However, concurrent cocaine and alcohol abuse is associated with serious medical problems. This drug combination was identified as the most frequent substance abuse pattern found among individuals presented to emergency rooms with substance abuse-related problems (Drug Abuse Warning Network, 1991). Also, epidemiological studies of cocaine fatalities have indicated that combined cocaine and alcohol abuse results in 18-fold increase in the risk of sudden death compared with cocaine abuse alone.[10] Although the observed effects of this drug combination may result from the pharmacological effects of cocaine in addition to those of alcohol, several investigations have shown that alcohol can significantly alter the pharmacokinetics of cocaine.[11−14]

Alcohol coadministration with cocaine in experimental animals and humans has been shown to inhibit the metabolism of cocaine,[15,16] increase the plasma and brain cocaine concentrations,[14] and lead to the formation of the pharmacologically active metabolite cocaethylene.[11−14] In controlled human studies, concurrent cocaine and alcohol administration have been shown to increase the plasma cocaine concentrations in addition to the formation of cocaethylene.[17,18] Cocaine area under the plasma concentration−time curve (AUC_p) and the maximum cocaine plasma concentration ($C_{p\ max}$) after administration of alcohol and cocaine were significantly higher than those after administration of cocaine only.[11−13,17] Because good correlation between the pharmacokinetics and pharmacological effects of cocaine has been reported,[19−21] alteration in cocaine pharmacokinetics has been implicated, at least in part, for the increased incidence of cocaine-related toxicities after combined abuse of cocaine and alcohol.

The primary objective of this study was to investigate the effect of alcohol coadministration on the pharmacokinetics and the pharmacological effects of cocaine in the rat. This objective was achieved by comparing cocaine absorption, distribution, and elimination when administered alone and in combination with alcohol. Both the neurochemical response measured as the change in dopamine concentration in the nucleus accumbens (N ACC) and the change in mean arterial blood pressure after the two treatments were

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10.1021/js980282p CCC: $18.00 Published on Web 03/12/1999

monitored simultaneously. This is the first investigation that examined the effect of alcohol coadministration on cocaine pharmacokinetics and pharmacological activities simultaneously in the same group of experimental animals.

Materials and Methods

Chemicals and Reagents—Cocaine hydrochloride, bupivacaine, 1-heptanesulfonic acid, and sodium fluoride were purchased from Sigma Chemical (St. Louis, MO). Acetonitrile and chloroform were supplied by Burdick and Jackson Laboratory (Muskegon, MI). The dehydrated-200 proof ethyl alcohol (USP) was purchased from McCormick Distilling (Weston, MO). Methanol, citric acid, EDTA, monobasic sodium phosphate, sodium hydroxide, and monobasic ammonium phosphate were obtained from J. T. Baker (Phillipsburg, NJ). All solvents were of high-performance liquid chromatographic (HPLC) grade, and all chemicals were of analytical reagent (AR) grade.

Animal Care and Preparation. Male Wistar rats (250−350 g, Simonsen Laboratories, Gilroy, CA) were maintained on a 12 h light/dark cycle and were given Purina chow pellets and water ad libitum for at least 7 days before use in the experiments. All operating procedures on animals were in accordance with the Guide for the Care and Use of Laboratory Animals (National Institutes of Health Publication No. 85-23, revised 1985) and were approved by the institutional animal care and use committee. The details of the animal preparation procedures were described previously.[22] Briefly, for the cocaine ip experiment, rats were prepared under aseptic condition while fully anesthetized by implanting a microdialysis cranial probe, cannulating the femoral arteries, and inserting abdominal and gastric catheters. For the cocaine iv experiment, all the procedures were similar except that the abdominal catheter was not implanted and only one femoral artery and one femoral vein were cannulated.

Cocaine and Alcohol Administration—A stock solution of cocaine (10 mg/mL) in normal saline was used for cocaine administration. For the ip cocaine experiment, the administered dose was 30 mg/kg, and for the iv cocaine experiment, the dose was 6.8 mg/kg. These doses were chosen because they are well below the cocaine dose that is lethal in 50% of the tested rats (LD_{50} 17 mg/kg for iv, and 75 mg/kg for ip, Material Safety Data Sheet, University of Washington, Seattle, 1995). Also, these doses should achieve measurable plasma and brain concentrations of cocaine and its metabolites over the period of the experiment. The alcohol dose (5 g/kg) was chosen to achieve an alcohol plasma concentration in the range of concentrations observed in humans after moderate drinking based on the reported alcohol pharmacokinetic parameters in rats.[23] Cocaine was administered ip via the abdominal catheter and iv via the femoral vein cannula, whereas alcohol was administered through the gastric catheter. This animal model allows cocaine and alcohol administration and collection of samples without the need to hold the rat, thereby avoiding the effect of animal handling on the monitored pharmacodynamic parameters.

Cocaine Pharmacokinetic and Pharmacodynamic Studies—*Cocaine ip Treatment*—Eight male Wistar rats were randomly chosen and were prepared following the surgical procedures just outlined. After the recovery period, each rat was treated with cocaine+normal saline and cocaine+alcohol in a balanced crossover experimental design with 48-h washout period between treatments. Four of the rats received cocaine+normal saline first followed by cocaine+alcohol after the washout period and the other four received cocaine+alcohol then cocaine+normal saline. In all the experiments, rats were pretreated with normal saline or alcohol 20 min before cocaine administration.

On the day of the experiment, one of the femoral artery cannulae was connected to a pressure transducer linked to a portable physiological monitor (Model VSM1, Physio-control, Redmond, WA) for monitoring the mean arterial blood pressure. Meanwhile, the effluent of the microdialysis probe (1 μL/min) was collected every 20 min into an HPLC autosampler vial spiked with 20 μL of dopamine mobile phase, and 5 μL was injected immediately into an HPLC with electrochemical detection (HPLC−EC) for dopamine analysis. This procedure was repeated until a stable basal dopamine concentration was detected (<10% difference in dopamine concentration in three consecutive collections). Once a stable dopamine baseline was achieved, the rat received either 10 g/kg of normal saline or 5 g/kg of alcohol (50% v/v in normal saline) through the gastric catheter. Twenty minutes later, 30 mg/kg of cocaine was administered ip through the abdominal catheter. This lag time was necessary to allow alcohol absorption into the systemic circulation before cocaine administration.[23] After cocaine administration, 10 blood samples, each of 0.2 mL, were collected through the femoral artery cannula at 2, 5, 10, 15, 30, 60, 90, 120, 180, and 240 min into vacutainers pretreated with heparin and sodium fluoride to avoid cocaine hydrolysis by the plasma esterases. Plasma samples were obtained by centrifugation and were stored at −20 °C until analysis for cocaine and its metabolites by HPLC with ultraviolet detection (HPLC−UV). The effluent of the microdialysis probe was continuously collected every 20 min throughout the experiment in HPLC autosampler vials containing 20 μL of the mobile phase for dopamine analysis (pH 4). This mobile phase was added to increase the stability of dopamine, cocaine, and cocaine metabolites in the collected samples. After mixing the vial content, 5 μL was injected immediately into the HPLC-EC system for dopamine analysis, and the remainder was analyzed for cocaine and its metabolites by HPLC−UV. The concentrations of cocaine and cocaine metabolites in the brain ECF were determined from the microdialysis probe effluent concentrations after correcting for the probe recovery, which was determined from an in vitro experiment.[24] The mean arterial blood pressure was continuously monitored during the entire experiment.

After the two treatments just described, four of these eight rats received a third treatment that consisted of alcohol (5 g/kg, 50% v/v in normal saline) through the gastric catheter. The purpose of this alcohol treatment was to determine the range of alcohol plasma concentrations achieved after alcohol administration during the pharmacokinetic experiment. Serial blood samples were obtained after alcohol administrations, and the plasma samples, each of 100 μL, were analyzed immediately for their alcohol content utilizing the Abbott ADx Analyzer (Abbott Diagnostic, Chicago, IL) as described previously.[13]

Cocaine iv Treatment. This experiment was performed to estimate the absolute bioavailability of cocaine after ip cocaine administration with and without alcohol pretreatment. Also, the results of this experiment were used to validate the pharmacokinetic model used in the analysis of the effect of alcohol pretreatment on cocaine pharmacokinetics. In this experiment, 12 male Wistar rats were randomly chosen and were prepared as already outlined.[22] After the recovery period, each rat received cocaine+normal saline and cocaine+alcohol in a balanced crossover design with a 48-h washout period between treatments. The rats received either normal saline (10 g/kg) or alcohol (5 g/kg, 50% v/v in normal saline) through the gastric catheter followed 20 min later by iv cocaine (6.8 mg/kg) via the femoral vein cannula. After cocaine administration, 10 blood samples, each of 0.2 mL, were collected through the femoral artery cannula at 2, 5, 10, 15, 30, 60, 90, 120, 180, and 240 min into vacutainers pretreated with heparin and sodium fluoride. Plasma samples were obtained by centrifugation and were stored at −20 °C until analysis for cocaine and its metabolites by HPLC−UV. The effluent of the microdialysis probe was continuously collected every 20 min and was analyzed for cocaine and its metabolites by HPLC−UV immediately after each collection.

Analytical Methods—*Cocaine and its Metabolites*—Plasma and microdialysis probe effluent were analyzed for cocaine and its metabolites by the method developed in our laboratory.[25] This is an isocratic HPLC method that involves extraction of cocaine and its metabolites from plasma samples with chloroform and utilizes bupivacaine as an internal standard. This method is sensitive enough to quantitate cocaine and its metabolites in concentrations as low as 25 ng/mL in 100-μL plasma samples, with a coefficient of variation of <10%. The brain ECF concentrations of cocaine and its metabolites were determined by the same method, except that the probe effluent was injected directly into the HPLC−UV system without any pretreatment.

Dopamine—The effluent of the microdialysis probe was injected directly into an HPLC system equipped with an electrochemical detector for dopamine analysis (Coulochem detector Model 5100A, guard cell Model 5020, and analytical cell Model 5014A, ESA, Bedford, MA). The mobile phase consisted of 0.1 M citrate, 0.075 M monobasic sodium phosphate, 36 mg/L of EDTA, 303 mg/L of 1-heptanesulfonic acid, and 5.5% methanol (v/v). The pH of the

mobile phase was adjusted to pH 4 with sodium hydroxide pellets. On the coulochem detector, the potential for the guard cell was set at −0.20 V, whereas those for detectors 1 and 2 were set at +0.30 and −0.15 V, respectively. Quantitation of dopamine was achieved on a Supelcosil LC-18-DB column (250 × 2.1 mm i.d., 5 μm), and the flow rate was 0.3 mL/min. The signal from detector 2 was analyzed with an electronic integrator (Hewlett-Packard, Model 3390, Palo Alto, CA). Because the change in dopamine ECF concentration after cocaine administration was expressed as percentage of baseline, dopamine probe recovery, which was necessary to calculate the actual concentration of dopamine in the brain ECF, was not determined.

Pharmacokinetic Analysis—A two-compartment pharmacokinetic model with elimination from the central compartment was used to analyze the effect of alcohol on cocaine absorption, distribution, and elimination after ip administration. This model assumes that cocaine absorption, distribution, and elimination follow first-order kinetics, and that the brain is part of the peripheral tissue compartment. The following equations were used to describe cocaine concentrations in the central (eqs 1 and 2) and the peripheral (eqs 3 and 4) compartments after a single ip (eqs 1 and 3) and iv administration (eqs 2 and 4):[26]

$$C_p = \frac{FD_{ip}k_a}{V_c}\left[\frac{(k_{21}-k_a)}{(\alpha-k_a)(\beta-k_a)}e^{-k_a t} + \frac{(k_{21}-\alpha)}{(k_a-\alpha)(\beta-\alpha)}e^{-\alpha t} + \frac{(k_{21}-\beta)}{(k_a-\beta)(\alpha-\beta)}e^{-\beta t}\right] \quad (1)$$

$$C_p = \frac{D_{iv}}{V_c(\alpha-\beta)}[(\alpha-k_{21})e^{-\alpha t} + (k_{21}-\beta)e^{-\beta t}] \quad (2)$$

$$C_b = \frac{FD_{ip}k_a k_{21}}{V_t}\left[\frac{e^{-k_a t}}{(\alpha-k_a)(\beta-k_a)} + \frac{e^{-\alpha t}}{(k_a-\alpha)(\beta-\alpha)} + \frac{e^{-\beta t}}{(k_a-\beta)(\alpha-\beta)}\right] \quad (3)$$

$$C_b = \frac{D_{iv}k_{12}}{V_t(\beta-\alpha)}(e^{-\alpha t} - e^{-\beta t}) \quad (4)$$

where D_{ip} and D_{iv} are cocaine doses for ip and iv administrations, F is cocaine bioavailability after ip administration, C_p and C_b are cocaine concentrations in the central (plasma) and tissue (brain ECF) compartments, respectively, V_c and V_t are volumes of distribution of the central and tissue compartments, k_a is cocaine first-order absorption rate constant after ip administration, k_{12} is the first-order transfer rate constant from the central to the tissue compartment, k_{21} is the first-order transfer rate constant from the tissue to the central compartment, k_{10} is the first-order elimination rate constant from the central compartment, and α and β are the hybrid first-order rate constants for the distribution and elimination processes, respectively.[26,27]

Plasma and brain ECF cocaine concentrations for each rat after ip cocaine with or without alcohol coadministration were fitted simultaneously to the two integrated equations that describe the plasma and brain ECF concentration−time profiles (eq 1 and 3). The pharmacokinetic model parameters were estimated by nonlinear regression analysis utilizing PCNONLIN (Version 4.0, SCI Software, Lexington, KY). Other pharmacokinetic parameters such as the total body clearance (*TBC*), the volumes of distribution at steady state and during the elimination phase (V_{dss} and $V_{d\beta}$), and the areas under cocaine plasma (AUC_p) and brain ECF (AUC_b) concentration−time curves were calculated from the estimated parameters.[27] The systemic bioavailability of cocaine after ip administration with and without alcohol pretreatment was calculated by comparing the corresponding AUC_p after iv and ip cocaine administrations.

Pharmacodynamic Analysis—*Neurochemical Response*—The sigmoid-E_{max} pharmacodynamic model was used to describe the relationship between the brain ECF cocaine concentration and the percent change in the brain ECF dopamine concentration.[22] The mathematical expression that describes the concentration−effect relationship for the sigmoid-E_{max} model is the following:

$$E = E_0 + \frac{E_{max}C_b^n}{EC_{50}^n + C_b^n} \quad (5)$$

where E is the effect measured as the percent change in dopamine basal concentration, E_0 is the baseline effect measured as the basal dopamine concentration, E_{max} is the maximum effect measured as the maximum change in dopamine concentration, EC_{50} is the brain ECF cocaine concentration when the observed effect is 50% of E_{max}, C_b is the brain ECF cocaine concentration, and n is the sigmoidicity factor. The pharmacodynamic model parameters were estimated by fitting the percent change in dopamine level and the cocaine concentration in the brain ECF at different time points to eq 5. The basal dopamine concentration was kept constant (100%) during the analysis. Nonlinear regression analysis was performed utilizing PCNONLIN.

Mean Arterial Blood Pressure Response—The relationship between the plasma cocaine concentration and the change in mean arterial blood pressure after ip cocaine administration followed counterclockwise hysteresis loop. The mean arterial blood pressure did not return to its baseline value at the end of the 4-h experiment.[21,22] This result indicates that under the condition of our investigation, there was no direct relationship between cocaine plasma concentration and the change in mean arterial blood pressure. Therefore, the indirect pharmacodynamic response model was utilized to characterize this relationship.[28,29] We chose the model that can describe indirect drug response resulting from inhibition of a mediator because cocaine effect on blood pressure results primarily from inhibition of catecholamine reuptake at the peripheral nerve endings leading to higher peripheral catecholamine concentration, which is responsible for the vasopressor effect of cocaine. The mathematical expression that describes the model for the change in the pharmacological response and the drug concentration is:

$$\frac{dR}{dt} = k_{in} - k_{out}\left(1 - \frac{I_{max}C_p^n}{IC_{50}^n + C_p^n}\right)R \quad (6)$$

where R is the observed response (percent change in mean arterial blood pressure), k_{in} is the apparent zero-order rate constant for response production, k_{out} is the first-order rate constant for response dissipation, I_{max} is the maximum inhibition of the factor that produces the effect, IC_{50} is the plasma cocaine concentration that leads to 50% inhibition of the factor that produces the effect, C_p is the plasma cocaine concentration at the time of the observed response, and n is the sigmoidicity factor.[28,29] The maximum response that will be achieved when D_{ip} is very large or IC_{50} approaches zero is the following:

$$R_{max} = \frac{R_0}{1 - I_{max}} \quad (7)$$

where R_{max} is the maximum response and R_0 is the basal response (100%).

The indirect pharmacodynamic model parameters were estimated by fitting the percent change in mean arterial blood pressure and the plasma cocaine concentration at different time points to eq 6. Nonlinear regression analysis was performed utilizing PCNONLIN.

Statistical Analysis—The pharmacokinetic and pharmacodynamic parameters obtained after cocaine+normal saline and cocaine+alcohol treatments were analyzed using the Statistical Analysis System (SAS Institute Inc., Cary, NC). The balanced crossover design of our investigation is equivalent to the two-way factorial experiment (2 × 2) with repeated measures on the cocaine treatment factor. The plasma and brain ECF cocaine concentration−time profiles, the percent change in dopamine brain ECF concentration−time profiles, and the percent change in mean arterial blood pressure−time profiles after the two treatments were analyzed with two-way analysis of variance with repeated measures on both factors using SAS. Treatments (cocaine+normal saline or cocaine+alcohol) and time were considered as the between subject-variability. Multiple comparison with Bonferroni correction was conducted to examine the difference between

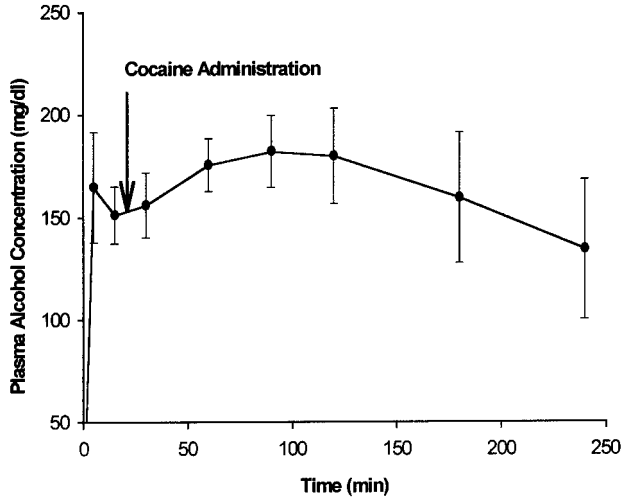

Figure 1—Plasma alcohol concentration–time profile after 5 g/kg of alcohol po ($n = 4$, data are presented as mean ± SE).

treatments at each time point. Differences of $P < 0.05$ were considered significant.

Results

Alcohol was rapidly absorbed after intragastric administration and its plasma concentration declined very slowly because alcohol elimination has been shown to follow zero-order kinetics in rodents.[13] The average plasma alcohol concentrations in the four rats that received 5 g/kg of alcohol intragastrically ranged from 140 to 180 mg/dL (0.14−0.18%) during the 4-h sampling period (Figure 1). This range of alcohol concentrations is similar to that observed in humans after moderate alcohol drinking.

The plasma concentration−time profile of cocaine after a single iv administration declined biexponentially with an average elimination half-life of 28.6 ± 3.5 min. After ip administration, cocaine was absorbed rapidly from the abdominal cavity, reaching the maximum plasma concentration within 10−15 min, and then the concentration declined, with an average elimination half-life of 26.3 ± 3.6 min. Meanwhile, the brain ECF cocaine concentration increased rapidly, reaching its maximum value within 10−20 min after iv administration and within 20−40 min after ip administration, and then declined parallel to the concentration in plasma (Figures 2A and 2B). Cocaethylene was detected in plasma and brain ECF only when cocaine was given with alcohol. Although other cocaine metabolites, including benzoylecgonine and norcocaine, were measured in both plasma and brain ECF in this study, the effect of alcohol on cocaine metabolic profile will be discussed in detail in a separate publication.

Pharmacokinetic studies that involved administered cocaine doses similar to those used in our investigation have shown that cocaine follows linear pharmacokinetics, which validates the first assumption of our proposed model.[13,14,30] The assumption that the brain is part of the peripheral compartment was validated by comparing the estimates for the pharmacokinetic parameters obtained from fitting the plasma concentrations to eq 2 with those obtained from fitting the plasma and brain concentrations simultaneously to eqs 2 and 4. Agreement between the estimated parameters using the two fitting procedures should indicate that the brain is indeed part of the peripheral compartment. The plasma and brain ECF concentrations obtained after iv cocaine administration were used in this validation. The average estimates for k_{12}, k_{21}, k_{10}, and V_c in 12 rats obtained from fitting eq 2 only

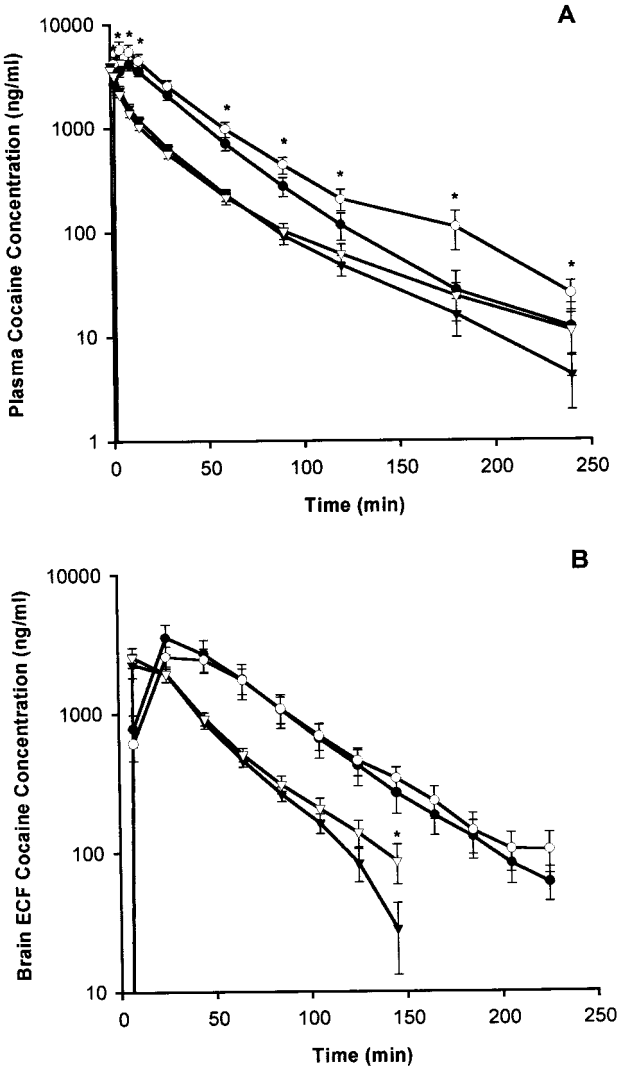

Figure 2—Plasma concentration–time profile of cocaine in plasma (A) and brain (B) after administration of 6.8 mg/kg cocaine iv (▼), 6.8 mg/kg of cocaine iv plus 5 g/kg alcohol po (▽), 30 mg/kg of cocaine ip (●), and 30 mg/kg of cocaine ip plus 5 g/kg alcohol po (○). Each point represents the mean ± SE from 12 rats (iv) and 8 rats (ip). Key: (*) significantly different from the cocaine+ normal saline treatment ($p < 0.05$).

were 0.094 min^{-1}, 0.097 min^{-1}, 0.075 min^{-1}, and 1.63 L/kg, respectively. The average estimates for k_{12}, k_{21}, k_{10}, and V_c in the same 12 rats obtained from fitting eq 2 and 4 simultaneously were 0.082 min^{-1}, 0.093 min^{-1}, 0.073 min^{-1}, and 1.76 L/kg, respectively. Statistical analysis showed that the estimated pharmacokinetic parameters from the two fitting procedures were not different. However, the precision of the parameter estimates was better when the plasma and brain concentrations were used simultaneously. These findings indicate that the brain is a representative part of the peripheral compartment in the proposed pharmacokinetic model and that fitting the plasma and brain data simultaneously improves the precision of the parameter estimation. The fact that the brain is part of the peripheral compartment in the pharmacokinetic model indicates that cocaine distribution to the brain is not instantaneous. As a result, the proposed pharmacokinetic model should adequately describe cocaine absorption, distribution, and elimination after ip administration. A representative example of the simultaneous fitting of the measured plasma and brain ECF cocaine concentrations after ip cocaine administration to eqs 1 and 3 is shown in Figure 3.

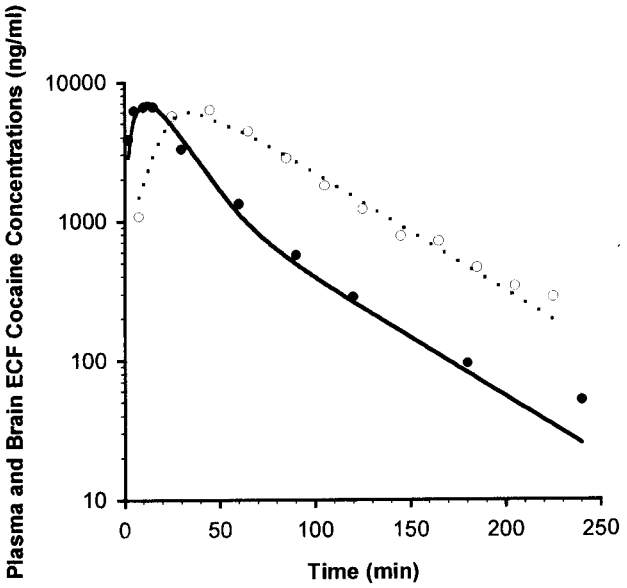

Figure 3—A representative example of the simultaneous fitting of the observed plasma (●) and brain ECF (○) cocaine concentration–time profiles after administration of 30 mg/kg of cocaine ip. The symbols represent the actual experimental data and the line represent the model-fitted curve.

Table 1—Pharmacokinetic Parameters for Cocaine after ip Administration in Wistar Rats (Mean ± SE, $n = 8$)

pharmacokinetic parameter	cocaine treatment: cocaine (ip)[a] + normal saline (po)	cocaine treatment: cocaine (ip)[a] + alcohol (po)
AUC_p (μg-min/mL)	154 ± 12	219 ± 34[c]
AUC_b (μg-min/mL)	224 ± 70	205 ± 47
AUC_b/AUC_p	1.35 ± 0.28	0.98 ± 0.17[c]
TBC (mL/min/kg)	203 ± 16[b]	158 ± 21[b]
t_{max} (min)	10.63 ± 0.63	7.50 ± 0.97[c]
$C_{p\,max}$ (ng/mL)	4100 ± 460	5900 ± 1060[c]
F	0.550 ± 0.044	0.754 ± 0.071[c]
k_a (min^{-1})	0.199 ± 0.045	0.276 ± 0.059
$\alpha_{t1/2}$ (min)	10.9 ± 2.1	10.2 ± 1.7
$\beta_{t1/2}$ (min)	26.3 ± 3.6	40.0 ± 8.1[c]
k_{12} (min^{-1})	0.021 ± 0.014	0.042 ± 0.023
k_{21} (min^{-1})	0.043 ± 0.006	0.036 ± 0.007
k_{10} (min^{-1})	0.056 ± 0.007	0.055 ± 0.011
V_c (L/kg)	2.12 ± 0.25	2.41 ± 0.37
V_{dss} (L/kg)	2.82 ± 0.37	4.11 ± 0.66[c]
$V_{d\beta}$ (L/kg)	4.07 ± 0.56	5.90 ± 0.91[c]
V_t (L/kg)	2.04 ± 0.48	3.50 ± 0.97[c]

[a] Cocaine dose, 30 mg/kg, ip; alcohol dose, 5 g/kg, po. [b] Presented as *TBC/F*. [c] Significantly different from the cocaine+normal saline treatment ($P < 0.05$).

The proposed pharmacokinetic model was used to examine the effect of alcohol coadministration on cocaine pharmacokinetics by comparing the pharmacokinetic parameters estimated after cocaine+normal saline and cocaine+alcohol. The estimated cocaine pharmacokinetic parameters after ip administration with and without alcohol pretreatment are summarized in Table 1. Alcohol pretreatment significantly affected the extent of cocaine absorption after ip cocaine administration. The absolute bioavailability of cocaine significantly increased from 0.550 ± 0.044 after cocaine+normal saline to 0.754 ± 0.071 after cocaine+alcohol. Although cocaine absorption rate, measured as the first-order absorption rate constant, was not significantly faster after alcohol pretreatment, the time to achieve the maximum plasma cocaine concentration was significantly shorter than that after administration of cocaine+normal saline. This result is an indication of a faster rate of cocaine absorption after alcohol pretreatment.

Table 2—Pharmacodynamic Parameters of Cocaine in Wistar Rats (Mean ± SE, $n = 8$)

pharmacodynamic parameter	cocaine treatment: cocaine (ip)[a] + normal saline (po)	cocaine treatment: cocaine (ip)[a] + alcohol (po)
A. neurochemical		
E_{max} (% of baseline)	850 ± 200	1550 ± 640
EC_{50} (ng/mL)	3400 ± 580	2000 ± 650[b]
n	1.23 ± 0.17	2.31 ± 0.29[b]
B. Cardiovascular		
k_{in} (% of baseline/min)	23.8 ± 5.1	36.0 ± 13.0
k_{out} (min^{-1})	0.218 ± 0.047	0.31 ± 0.11
I_{max}	0.304 ± 0.033	0.307 ± 0.035
IC_{50} (ng/mL)	6700 ± 2100	5600 ± 710
R_{max} (% of baseline)	146 ± 6.9	148 ± 8.9
n	3.0 ± 1.5	3.6 ± 1.9

[a] Cocaine dose, 30 mg/kg; alcohol dose, 5 g/kg. [b] Significantly different from the cocaine+normal saline treatment group ($p < 0.05$).

Alcohol pretreatment also resulted in a significant prolongation of cocaine elimination half-life from 26.3 ± 3.6 min after cocaine+normal saline to 40.0 ± 8.1 min after cocaine+alcohol treatment. Similarly, the estimated cocaine elimination half-life after iv administration significantly increased from 28.6 ± 3.5 min after cocaine+normal saline to 37.3 ± 4.7 min after cocaine+alcohol. The estimated apparent *TBC* of cocaine decreased from 203 ± 16 mL/min/kg after cocaine+normal saline to 158 ± 21 mL/min/kg after cocaine+alcohol; however, this difference was not significant. Another interesting finding of this study is that the brain-to-plasma distribution ratio, measured as the ratio of the cocaine AUC in the brain ECF to the cocaine AUC in plasma, decreased significantly from 1.35 ± 0.28 after cocaine+normal saline to 0.98 ± 0.17 after cocaine+alcohol. Also, alcohol pretreatment resulted in a significant increase in the volume of distribution of cocaine.

After cocaine administration, the brain ECF dopamine concentration increased and reached its maximum value within 20−40 min, then it gradually declined to its baseline value at the end of the 4-h experiment period. Dopamine concentration−time profile followed closely the cocaine concentration−time profile in the N ACC. Alcohol coadministration with cocaine caused significantly higher dopamine concentrations in the N ACC, and the rate of decline of dopamine concentration to its baseline level was slower compared with that after cocaine+normal saline (Figure 4A). The relationship between the brain ECF cocaine concentration and the percent change in dopamine concentration was described using the sigmoid-E_{max} pharmacodynamic model. A representative example of the sigmoid-E_{max} model-fitted curve is shown in Figure 4B. The average estimate for E_{max} increased by ≈80% when alcohol was administered with cocaine, however, this difference was not statistically significant. Also, after cocaine+alcohol, the estimated EC_{50} was significantly smaller and the sigmoidicity factor *n* was significantly larger than those after cocaine+normal saline. A summary of the pharmacodynamic parameters is shown in Table 2.

The mean arterial blood pressure increased rapidly after cocaine administration and then declined slowly and did not return to its baseline value at the end of the 4-h experiment (Figure 5A). Because alcohol alone caused, on average, a 5−10% decrease in blood pressure, we partitioned this effect from the combined effect of cocaine+alcohol when these drugs were administered together (Figure 5A). The corrected percent change in mean arterial blood pressure−time profile was used for pharmacodynamic

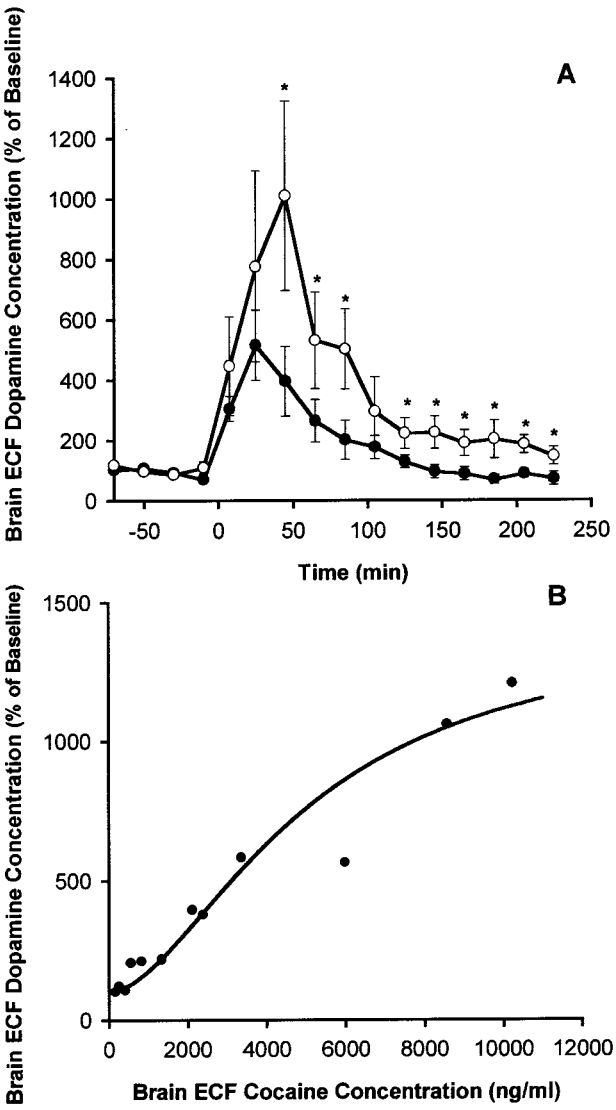

Figure 4—(A) Brain ECF dopamine concentration–time profiles after administration of 30 mg/kg of cocaine ip (●) and 30 mg/kg of cocaine ip plus 5 g/kg of alcohol po (○). Each point represents the mean ± SE from 8 rats. (B) A representative example of the relationship between the percent change in brain dopamine concentration and cocaine brain ECF concentration after ip administration of 30 mg/kg cocaine to the rat. The symbols represent the observed values and the line represents the sigmoid-E_{max} model-fitted curve. Key: (*) significantly different from the cocaine+normal saline treatment ($p < 0.05$).

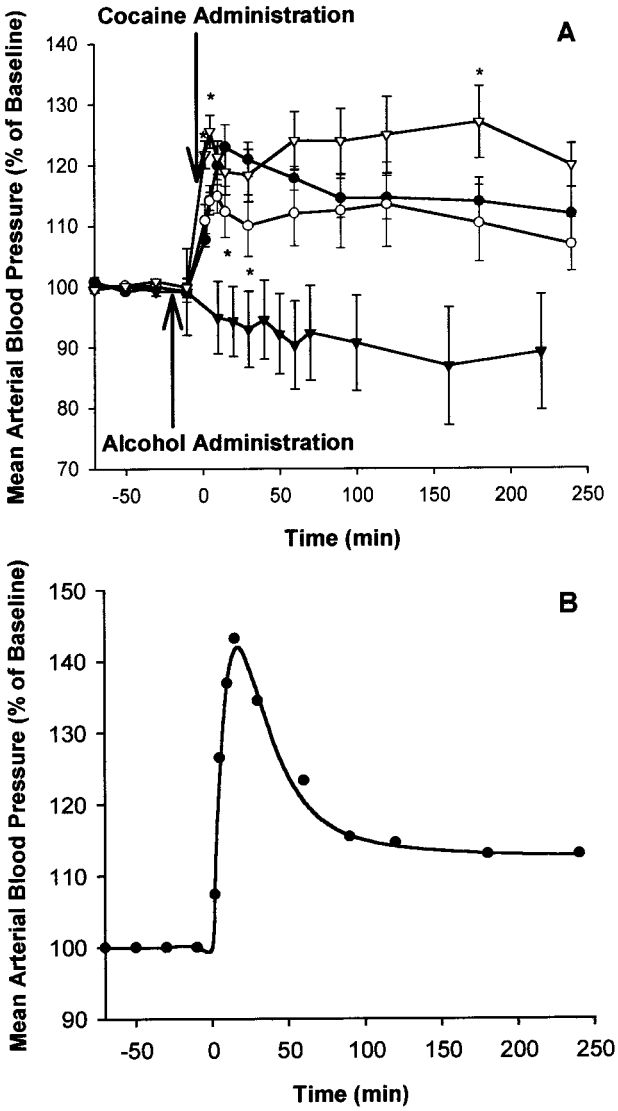

Figure 5—(A) Percent change in mean arterial blood pressure after administration of 30 mg/kg of cocaine ip (●), 30 mg/kg of cocaine ip plus 5 g/kg of alcohol po (○), and 5 g/kg of alcohol po (▼). The mean arterial blood pressure–time profile with cocaine and alcohol coadministration after partitioning the effect of alcohol is also presented (▽). Each point represents the mean ± SE from 8 rats (only 4 rats for alcohol po). (B) A representative example of the percent change in mean arterial blood pressure–time profile after ip administration of 30 mg/kg cocaine to the rat. The solid circles (●) represent the observed values and the line represents the indirect inhibitory pharmacodynamic response model-fitted curve. Key: (*) significantly different from the cocaine+normal saline treatment ($p < 0.05$).

modeling. A representative example of the observed values and the indirect inhibitory pharmacodynamic response model-fitted curve is shown in Figure 5B. Table 2 shows that the estimated parameters for the proposed pharmacodynamic model were not different after cocaine+normal saline and cocaine+alcohol.

Discussion

The pharmacokinetic model used to describe cocaine disposition in our investigation is a two-compartment model with first-order absorption, distribution, and elimination. The proposed two-compartment pharmacokinetic model used in our investigation was adequate in describing cocaine pharmacokinetics as indicated by the good agreement between the experimental data points and the model predicted curves. Examination of the cocaine plasma concentration−time profile and the brain ECF concentration−time profile showed the existence of a short delay in the appearance of cocaine in the brain. This delay represents the distribution of cocaine to the brain, which has been shown to be part of the peripheral compartment in the proposed model. The experimental design in the current investigation involved serial sampling of both plasma and brain ECF that represent the central and the peripheral compartments, respectively. This design allowed characterization of the absorption, distribution, and elimination of cocaine after ip administration, and examination of the effect of alcohol pretreatment on these processes.

Cocaine undergoes significant presystemic elimination, which is the main cause of its incomplete bioavailability after ip administration. Alcohol coadministration significantly increased the systemic bioavailability of cocaine due to the inhibition of cocaine presystemic metabolism. This conclusion is indicated because the maximum concentration of benzoylecgonine, one of the major cocaine metabolites, was lower after cocaine+alcohol administration in the

current study (data not shown) and in pervious investigations.[13,17] Similar inhibition of the presystemic metabolism by alcohol has been reported for drugs that undergo significant first-pass effect.[31,32] This increase in cocaine bioavailability was reflected by the significant increase in its *AUC* and $C_{p\ max}$ after cocaine+alcohol compared with those values after cocaine+normal saline. Although the increase in cocaine first-order absorption rate constant was not significant after cocaine+alcohol, the time to achieve maximum cocaine plasma concentration was significantly shorter. This result indicates that alcohol may enhance the rate of cocaine absorption, which is consistent with what we have reported previously.[13]

Alcohol coadministration significantly increased the volume of distribution of cocaine. The results of our investigation showed that V_c did not change due alcohol administration with cocaine, however both V_{dss} and $V_{d\beta}$ increased significantly. Cocaine has been shown to bind primarily to albumin and alpha-1-acid glycoprotein in serum.[33] Also, cocaine is extensively distributed to tissues such as kidney, brain, liver, heart, and placenta.[34] The significant increase in cocaine volume of distribution due to alcohol coadministration is caused by increased cocaine tissue distribution, which may have resulted from altering the binding of cocaine in plasma and tissues.[35] These results are not contradictory to the decreased brain-to-plasma *AUC* ratio when cocaine was administered with alcohol. Because the microdialysis technique used for the determination of cocaine brain ECF concentration measures only the free (unbound) cocaine concentration in the brain ECF. This free concentration is dependent on the total cocaine concentration and the cocaine bound fraction in the brain, which may be altered due to alcohol coadministration. We have previously reported that alcohol coadministration with cocaine increased the brain ECF concentration of cocaine.[14] However, alcohol was administered by a constant-rate iv infusion in that study, and the plasma alcohol concentration achieved at the end of the 4-h experiment period was on average 365 mg/dL. This result may suggest that more severe alcohol intoxication can lead to higher brain and plasma cocaine concentrations that may augment cocaine pharmacological effects and toxicity.

Alcohol coadministration has been shown to inhibit cocaine metabolism in vivo and in mouse and human liver preparations in vitro.[15−17] The decrease in *TBC* due to alcohol coadministration in our investigation was barely insignificant. However, cocaine elimination half-life was significantly prolonged due to alcohol coadministration. The increase in cocaine volume of distribution in addition to the insignificant reduction of the cocaine TBC contributed to the significantly prolonged cocaine half-life. These findings suggest that the enhanced cocaine systemic bioavailability and the prolonged cocaine elimination half-life are the major factors responsible for the significantly higher and prolonged cocaine plasma concentrations after cocaine+alcohol.

It has been reported previously that drug abusers often experience more intense and longer lasting euphoric effect after simultaneous use of cocaine and alcohol.[9] Controlled human studies have shown that, compared with either cocaine or alcohol administration alone, the combination of cocaine and alcohol seemed to produce more marked subjective effects especially in the feelings related to well-being.[17,18] Results from the current investigation also showed that the increase in dopamine concentration in the N ACC after cocaine+alcohol was significantly higher and its rate of decline to the baseline was slower than that after cocaine+normal saline. Several factors may contribute to the higher dopamine concentration in the N ACC. Cocaethylene, a pharmacologically active metabolite formed only when both cocaine and alcohol are administered, has been shown to possess cocaine-like effects and can increase dopamine concentration after administration in experimental animals.[34−38] Another contributing factor may be related to alcohol administration because alcohol has been shown to increase dopamine brain concentrations after acute or chronic administrations in experimental animals.[39] It is also possible that the increased tissue distribution of cocaine due to alcohol pretreatment may result in higher (bound + free) brain tissue concentration of cocaine, which can lead to higher dopamine concentrations.

The relationship between cocaine brain ECF concentration and the change in N ACC dopamine level can be described by the sigmoid-E_{max} pharmacodynamic model.[22] Our pharmacodynamic analysis showed that the estimated E_{max} was higher after cocaine+alcohol compared with after cocaine+normal saline, however, this difference was not significant. On the other hand, EC_{50} was significantly lower after cocaine+alcohol compared with after cocaine+normal saline. This result means that the same brain ECF cocaine concentration will produce higher neurochemical response after coadministration of alcohol, which is consistent with the more intense and longer lasting euphoric effects experienced by subjects after combined abuse of cocaine and alcohol.[9] This higher response may be caused by the pharmacologically active metabolite cocaethylene, which is formed only when cocaine is administered with alcohol. The contribution of cocaine metabolites to the observed pharmacological activities after administration of cocaine and alcohol will be discussed in detail in a separate publication. Other possibilities for the enhanced neurochemical responses when cocaine is administered with alcohol may include the effect of alcohol and the increased cocaine brain tissue distribution as was discussed previously.

The cardiovascular activities of cocaine are mainly due to its sympathomimetic effects. These include an increase in blood pressure, QRS duration, and heart rate.[1] However, at higher cocaine concentrations, the sodium channel blocking effect of cocaine can slow the cardiac conduction and result in slower heart rate.[5] In this study, the immediate increase in mean arterial blood pressure achieved after cocaine administration is mainly due to the sympathomimetic vasopressor effect of cocaine. Alcohol coadministration did not have any significant effect on the change in the mean arterial blood pressure after cocaine administration. Studies conducted in humans also showed that the change in arterial systolic and diastolic blood pressures after administration of cocaine and alcohol was similar to that of cocaine only.[17] The lack of difference in the vasopressor response after the two treatments despite the higher cocaine plasma concentrations after cocaine+alcohol may be attributed to the effect of alcohol on the cardiovascular system. Alcohol caused an average 5−10% reduction in the mean arterial blood pressure in the rats that received alcohol only. This reduction means that the change in the mean arterial blood pressure in response to cocaine administration was larger after cocaine+alcohol (if the effect of alcohol is partitioned) compared with that after cocaine+normal saline. The higher and the prolonged cocaine plasma concentration in addition to the formation of cocaethylene after cocaine+alcohol treatment may be responsible for the higher response to cocaine after cocaine+alcohol.

Several previous studies reported that the relationship between plasma cocaine concentration and the change in the mean arterial blood pressure showed a counterclockwise hysteresis.[21,22,40] This hysteresis indicates that there is no direct relationship between cocaine plasma concentration and the change in the mean arterial blood pressure.

When direct concentration−effect relationship does not exist, indirect pharmacodynamic response models,[28,29] or the use of an effect compartment may be useful in the pharmacodynamic analysis.[41] The indirect pharmacodynamic response model used to describe the relationship between cocaine plasma concentration and the change in blood pressure adequately characterized this relationship. This adequacy is evident from the agreement between the observed results and the model-fitted curve. Table 2 shows that the maximum inhibitory effect of cocaine on neurotransmitter reuptake was increased by 2.30% when alcohol was administered with cocaine. Also, alcohol coadministration increases the potency of cocaine as reflected by the 20% reduction in IC_{50}. This difference in the blood pressure response to cocaine after the two treatments may have clinical and biological significance despite the fact that the difference is statistically insignificant.[6] This difference may also explain the increased incidence of cardiovascular toxicity after abusing this drug combination.

The cocaine dose used in the ip administration experiment (30 mg/kg) is in the range of doses used frequently in the pharmacological investigations of cocaine. The plasma cocaine concentrations achieved after administration of this dose was higher than the plasma cocaine concentration observed in human studies. However, this dose was well tolerated by the rats and there was no visible evidence of acute adverse effects. The choice of this dose was necessary to precisely determine the pharmacokinetic behavior of cocaine in plasma and brain ECF and to characterize the cocaine concentration−pharmacological effects relationship over a wide range of cocaine concentrations. It will be important to determine if the outcome of the interactions between cocaine and alcohol is dependent on the dose of cocaine and/or alcohol.

In conclusion, alcohol coadministration increases the rate and extent of cocaine absorption after ip administration and increases the tissue distribution of cocaine as manifested by the increase in cocaine volume of distribution. Meanwhile, cocaine elimination is inhibited resulting in longer cocaine half-life. The combined effect of these pharmacokinetic changes produces higher and prolonged cocaine plasma concentrations. The pharmacologically active metabolite cocaethylene is detected in both plasma and brain ECF only when cocaine and alcohol are administered together. Alcohol coadministration also augments the pharmacological activities of cocaine, especially its CNS effects. Because of the existence of good relationships between cocaine brain and plasma concentrations and the neurochemical and cardiovascular responses to cocaine administration, the changes in cocaine pharmacokinetics are, at least partially, responsible for the changes in cocaine effects after administration of this drug combination.

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Acknowledgments

This work was supported by a grant from the National Institute of Neurological Disorder and Stroke (NS/OD36399-01).

JS980282P