Published in final edited form as:

Am J Addict. 2016 August ; 25(5): 392–399. doi:10.1111/ajad.12402.

Cocaine Cardiovascular Effects and Pharmacokinetics after Treatment with the Acetylcholinesterase Inhibitor Donepezil

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Abstract

Background—In rodents, cholinesterase inhibitors can cause sustained decreases in the reinforcing effects of cocaine. Nonetheless, cocaine is metabolized by butyrylcholinesterase (BuChE), raising concerns that cholinesterase inhibition could increase its peripheral concentrations, perhaps augmenting toxicity. Although donepezil is approved for use in patients and selective for inhibiting acetylcholinesterase over BuChE, no studies have reported cocaine bioavailability in human subjects receiving donepezil.

Methods—Twelve cocaine-dependent veterans received three days of treatment with either oral placebo or 5 mg daily of donepezil, followed by cross-over to the opposite treatment. During both oral treatments, double-blind intravenous cocaine was administered at 0.0, 0.18, 0.36 mg/kg in a laboratory setting, followed by determinations of heart rate, blood pressure, and plasma concentrations of cocaine and major metabolites.

Results—Intravenous cocaine produced dose-related increases in systolic blood pressure that were most pronounced over the initial 30 minutes after treatment. Oral donepezil attenuated drug-induced elevations of systolic blood pressure following low-dose cocaine (0.18 mg/kg). No significant difference in blood pressure following treatment with placebo or donepezil after high-

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Declaration of Interest

The authors report no conflicts of interest, and they alone are responsible for the content and writing of this paper.

dose cocaine (0.36 mg/kg). Peak values of blood pressure and heart rate were unaffected by donepezil. Plasma concentrations of cocaine and metabolites did not differ in donepezil- and placebo- treated participants.

Conclusions and Scientific Significance—We conclude that donepezil can attenuate drug-induced increases in systolic blood pressure following low-dose cocaine, but does not otherwise modify the cardiovascular effects of intravenous cocaine. Clinically significant changes in cocaine bioavailability and cardiovascular effects do not occur following this dose of donepezil.

Keywords

Acetylcholine; Cardiovascular System; Cholinesterase Inhibitor; Cocaine; Cocaine-Related Disorders; Drug Metabolic Detoxification; Pharmacokinetics

Introduction

Cocaine is an addictive stimulant that can cause psychiatric disorders, seizures, stroke, and cardiovascular toxicity.¹ The annual prevalence of adult cocaine usage is estimated at 1.5% of North Americans, which is particularly high relative to its world-wide pattern of use.² It is a leading cause of emergency room visits and excess mortality, especially when used by injection or in combination with heroin.³ Individuals who die of cocaine overdose have greater cardiovascular and cerebrovascular pathology compared to those with fatal opiate overdose or non-drug suicide mortality. Correcting for age and demographics, cocaine-induced mortality was associated with an increased incidence of left ventricular hypertrophy, ischemic heart disease, and aortic or cerebrovascular atherosclerosis.⁴ Use of cocaine is also associated with disturbances in heart rhythm, often involving the ventricle and its repolarization.⁵ Cocaine-induced central nervous system toxicity can include stroke, subarachnoid and intracerebral hemorrhage, and cerebral ischemia.⁶ Individuals with pre-existing vascular malformation or aneurysm are at increased risk for these events. There is evidence that cocaine has pro-thrombotic properties that may promote cardiac or brain ischemia.⁷ Cocaine-induced vasospasm, impaired hemostasis and platelet function, as well as decreased cerebral blood flow, have also been implicated as possible mechanisms of cocaine-induced cardiovascular toxicity.⁸

The neurotransmitter acetylcholine plays a key role in drug reinforced behavior.⁹ Stimulation of nicotinic or muscarinic cholinergic inputs by acetylcholine can enhance neurotransmitter release by mesolimbic dopamine neurons which project to the nucleus accumbens and other brain regions, and underlie cocaine self-administration. Cocaine reinforcement activates cholinergic neurons in the nucleus accumbens, with the number of activated cells in the nucleus accumbens shell region correlated with the amount of drug self-administered.¹⁰ Elevated levels of acetylcholine in the nucleus accumbens may serve as a neural indicator of aversiveness, or as a signal that inhibits appetitive behaviors.¹¹ Synaptic levels of acetylcholine are regulated by cholinesterases that catalyze its inactivation. Mammalian brain contains two forms of cholinesterase, acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE). Treatment with cholinesterase inhibitors or cholinergic agonists can improve learning and memory in animals that have been exposed to cholinergic neurotoxins and patients with Alzheimer's disease. The physiologic role of BuChE is

unclear, but it can metabolize cocaine and other exogenous compounds and appears to contribute to degradation of acetylcholine.¹² Donepezil, is a reversible, long-acting, centrally-selective piperidine-type cholinesterase inhibitor that is structurally different from other clinically available compounds.¹³ In rat brain homogenate, donepezil produces a concentration-dependent inhibition of AChE with a 50% inhibitory concentration of 11.8 nM, with only weak inhibition of BuChE.¹⁴ The greater selectivity of donepezil for central AChE activity in rats is reflected by its greater potency for inducing yawning (mediated through central cholinergic receptors) relative to increases in tremor (mediated through peripheral receptors). Animal studies have also shown concentrations of donepezil in brain exceed values in plasma by more than six-fold,¹⁵ but comparable human data are not available.

Pretreatment with donepezil and other cholinesterase inhibitors can attenuate cocaine reinforced behavior in non-human primates, rats, and mice.¹⁶ Nonetheless, human studies have not shown cholinesterase inhibition to be a successful treatment for cocaine dependence in either a laboratory or outpatient setting.¹⁷ This may be due to limitations in the dose of inhibitor utilized. In addition, the safety of cholinesterase inhibitors remains an important issue. Given the high rate of relapse in treatment-seeking individuals, it is assumed that cholinesterase inhibitors will be coadministered with cocaine in a significant number of patients. A medication that produced greater availability of cocaine through BuChE inhibition could potentiate cocaine-induced brain and cardiac toxicity. Both cocaine and cholinergic agents can have pronounced effects on the autonomic nervous system, increasing the likelihood of drug interactions. The present study was conducted to examine the effects of donepezil pretreatment on cardiovascular measures, plasma concentrations of cocaine, and cocaine metabolites. Given the lack of any previous studies of its interaction with cocaine, we evaluated treatment with 5 mg daily of donepezil, the recommended dose for initial treatment in Alzheimer's disease.

Methods

Design and Participants

Detailed methods and changes in the subjective effects of cocaine after donepezil treatment in this trial have been previously reported.^{17,18} Briefly, we conducted an inpatient double-blind crossover design to evaluate the interaction between intravenous cocaine and oral donepezil in twelve cocaine-dependent veterans.

Prior to enrollment, participants were medically screened by physical and mental health exams performed by a physician and routine chemistry, blood-count, and urinalysis studies. All participants met criteria for cocaine dependence, according to the Diagnostic and Statistical Manual of Mental Disorders, 4th text revision edition.¹⁹ To enhance monitoring, improve compliance, and prevent illicit drug use, dosing and washout periods were conducted while subjects were admitted to an inpatient medical floor over a 15-day period. An initial session was performed to ensure that participants tolerated intravenous cocaine. Two subsequent sessions were conducted three hours following a third daily dose of donepezil (5 mg) or oral placebo. The different oral treatments were separated by a three-day washout period. Each laboratory session included four injections administered at one-

hour intervals, two of intravenous placebo, one of low-dose cocaine, and one of high-dose cocaine (0.0, 0.18 and 0.36 mg/kg, respectively). To mitigate potential toxicity when combined with donepezil, the low and high doses of cocaine were always administered in an ascending order, separated by an injection of intravenous placebo. This ensured that patients tolerated low-dose cocaine combined with donepezil, before being advanced to high-dose cocaine with donepezil. Because of the expense of assays, plasma samples for determination of cocaine and metabolites were only collected after high-dose cocaine. To maintain the blind, blood samples were collected after both high-dose cocaine and its corresponding intravenous placebo. During double-blind oral dosing, participants were randomized in equal numbers to receive intravenous treatments in one of two treatment orders: placebo, 0.18 mg/kg of cocaine, placebo, and 0.36 mg/kg of cocaine; or 0.18 mg/kg of cocaine, placebo, 0.36 mg/kg of cocaine, and placebo. A 20-gauge intravenous catheter was inserted into the antecubital fossa on the dominant side for administration of cocaine and blood sampling. Saline or cocaine was administered by intravenous push over two minutes, with a physician present.

Study procedures were reviewed and approved by the Kansas City VA Human Subjects Committee, with all subjects providing written informed consent. Healthy, regular users of cocaine between 18 and 50 years of age were included. All participants were male, with a mean age of 46.4 years, ± 0.8 years standard error. On average, they reported using cocaine on 14.3 ± 2.2 days of the previous month, having used cocaine for a duration of 21.0 ± 1.3 years, with $\$191.7 \pm 37.2$ per week current expenditure for cocaine. Participants reported having consumed alcohol for an average of 22.0 ± 2.5 years, and consuming an average of $10.3 \pm$ standard drinks per week at the time of their participation. In order to participate, they were required to provide a recent urine sample that tested positive for the presence of benzoylecgonine. Only individuals who were not actively seeking medical treatment for cocaine dependence were included. Those with a history of a medical adverse reaction to cocaine, a current psychiatric disorder other than drug abuse, or unstable medical condition were excluded. Additional demographic detail on the study participants has been previously reported.¹⁷

Cardiovascular Measures

Before and after intravenous placebo or cocaine, each subject's physiologic responses were closely monitored using continuous electrocardiographic recording and frequent blood pressure and heart rate measures by a Datascope Passport monitor. Blood pressure and heart rate were recorded at the midpoint and completion of each intravenous infusion; and at 4, 6, 8, 10, 15, 20, 30, 40, and 50 minutes after dosing.

Cocaine Plasma Concentrations

Participants received an initial 0.18 mg/kg dose of cocaine over two minutes, after which cocaine and its metabolites were not determined. Two hours after the first injection, a second 0.36 mg/kg injection of cocaine was administered by slow injection over two minutes. Plasma determinations of cocaine, benzoylecgonine, ecgonine methyl ester, and norcocaine were made at baseline and 10, 15, 30, 60, 120, 240, and 480 minutes after the start of the second intravenous injection. Blood was collected into Vacutainer tubes containing additives

to inhibit hydrolysis of cocaine by plasma cholinesterases (Becton Dickinson catalog number 367922, 4 ml aliquots of blood were each collected into tubes containing 10 mg of sodium fluoride and 8 mg of potassium oxalate).²⁰ After separation of plasma by routine methods, samples were frozen at -70°C until assay. Plasma levels of cocaine and metabolites were assayed by liquid chromatography-tandem mass spectrometry with a lower limit of quantitation of 2.5 ng/mL.^{21,22}

Data Analysis and Pharmacokinetics

For cardiovascular measures, statistical comparisons were done using Systat software (version 13, Evanston, IL), with results reported as group means $\pm$ standard error. Analysis of variance (ANOVA) was performed using oral dose (placebo or 5 mg daily of donepezil) and intravenous dose (placebo, low-dose cocaine, and high-dose cocaine) as factors. Post hoc contrasts were accomplished by either additional ANOVAs, or through *t*-tests after applying the correction by Sidak.²³ Planned analyses made comparisons across three broad areas that included systolic blood pressure, diastolic blood pressure, and heart rate. Estimating a 40% correlation between these interrelated measures, and applying a Sidak correction, yields a type I error (alpha) of 0.026.

The pharmacokinetic parameters maximum plasma concentration (C_{max}), and time to reach C_{max} (T_{max}) were determined from inspection of the data. Area under the plasma concentration versus time curve (AUC), area under the first moment curve (AUMC), mean residence time (MRT), apparent volume of distribution at steady-state (V_{SS}), elimination rate constant (k_e), half-life ($t_{1/2}$), and total body clearance (CL) were estimated from plasma concentration versus time data utilizing PCNONLIN 4.2 (SCI Software, Apex, NC). A non-compartmental model was used to fit all plasma concentration versus time data. MRT (min) was calculated from the quotient (AUMC/AUC), and CL (mL/min) from the quotient (Dose/AUC). V_{SS} was calculated from the product (MRT $\times$ CL). The $t_{1/2}$ was calculated from the quotient ($\ln 2/k_e$). Plasma concentrations of cocaine and metabolites were also compared by analysis of variance, using all available data points.

Results

Cardiovascular measures

Neither baseline blood pressure nor heart rate differed after participants received three days of oral placebo or donepezil (Table 1). Change in systolic blood pressure over time after different treatments is shown in Figure 1. Drug-induced increases in systolic blood pressure varied significantly with dose of cocaine [$F(2,484) = 136.3$; $p < 0.001$] but not donepezil [$F(1,242) = 3.26$; p not significant]. Nonetheless, a significant interaction of cocaine and donepezil doses was observed [$F(2,484) = 8.91$; $p < 0.001$]. Intravenous cocaine produced expected dose-related increases in systolic blood pressure that were most pronounced over the initial 30 minutes after treatment. Pretreatment with donepezil attenuated drug-induced elevations of systolic blood pressure following low- but not high- dose cocaine ($F(1,262) = 15.3$; $p < 0.001$, Figure 1B). Diastolic blood pressure and heart rate also showed trends for cocaine-induced increases, but were unaffected by donepezil treatment (data not shown).

Maximum or peak values for blood pressure and heart rate after different treatments are shown in Figure 2. Oral donepezil treatment did not modify peak values for any of the cardiovascular measures. Relative to treatment with intravenous placebo, high-dose cocaine increased all three peak measures combined across both oral treatments.

Cocaine Pharmacokinetic Profile

Prior to receiving a second cocaine infusion (two hours after an initial dose of cocaine for that session), cocaine was detectable in plasma from all except one placebo-treated subject, and two donepezil-treated subjects. All participants had detectable concentrations of cocaine in plasma collected between 10 and 120 minutes after intravenous dosing. At the four hour-time point, plasma cocaine was detectable in five subjects treated with oral placebo and five subjects treated with donepezil. None of the subjects evaluated had detectable plasma concentrations of cocaine at the eight-hour time point.

Group means for plasma concentrations of cocaine after oral placebo or donepezil treatment are shown in Figure 3B. All participants had plasma cocaine detectable at a sufficient number of time points to derive pharmacokinetic parameters. Visual inspection and curve fitting of log-transformed plasma concentrations of cocaine suggested a one-compartment disposition in some subjects, with data from other participants more consistent with a two-compartment model. Neither a single- nor dual- compartment model was adequate to account for data from all participants. Accordingly, a pure non-compartmental analysis was used to derive pharmacokinetic parameters, which are shown in Table 2. All subjects exhibited a time of maximal concentration (T_{max}) of 10 minutes. For pharmacokinetic parameters, we observed substantial inter- and intra- individual (across session) variation. Donepezil treatment did not alter plasma concentrations of cocaine, benzoylecgonine, or ecgonine methyl ester; or any of the derived pharmacokinetic parameters. For values combined across both oral treatments, plasma benzoylecgonine was increased for all time points after dosing with high-dose cocaine, with cocaine and ecgonine methyl ester increased for all time points up to 2 and 4 hours following dosing, respectively.

Cocaine Metabolites

Plasma concentrations of cocaine metabolites are shown in Panels A and C of Figure 3, with pharmacokinetic parameters reported Table 2. As for the parent cocaine molecule, neither concentrations of benzoylecgonine nor ecgonine methyl ester differed after donepezil treatment. Benzoylecgonine was detectable in plasma at all time points in both placebo- and donepezil treated subjects. Because less than three values were available in its terminal phase, elimination rate constants could not be calculated in two placebo and three actively-treated participants. Benzoylecgonine was eliminated with a half-life of approximately six hours, which was unaffected by donepezil treatment.

Prior to the second cocaine infusion, ecgonine methyl ester was detectable in plasma from seven placebo-treated and five donepezil-treated subjects. After the second cocaine infusion, ecgonine methyl ester was detectable in plasma from most subjects, with no differences in the number of detectable samples in placebo- and donepezil- treated subjects. Because less than three values were available in its terminal phase, elimination rate constants could not be

calculated in three placebo and four actively-treated participants. Ecgonine methyl ester was eliminated with a half-life of approximately five hours, which was again not altered by donepezil treatment. Norcaine, a minor metabolite of cocaine, was not detected in plasma from any subject.

Discussion

This study shows that patients who received donepezil prior to a low dose of intravenous cocaine exhibited lower drug-induced increases in systolic blood pressure. In contrast, increases in blood pressure after treatment with high-dose cocaine were not affected by donepezil treatment. Heart rate and diastolic blood pressure were unaffected by either dose of cocaine. Plasma concentrations of cocaine and major metabolites also did not differ in subjects receiving either donepezil or oral placebo. The pattern of metabolites matches previous reports of intravenously administered cocaine.^{22,24} As previously reported, treatment with donepezil in this trial increased some of the positive subjective effects of cocaine while augmenting dysphoric effects and somatic symptoms.¹⁷ Overall, these findings indicate that donepezil administered at 5 mg daily modifies the subjective and cardiovascular actions of cocaine, without enhancing drug-induced elevations in heart rate or blood pressure, or increasing the availability of cocaine in plasma.

Despite a large number of clinical trials evaluating many potential agents, no medication has been generally accepted or approved by the Food and Drug Administration to assist dependent individuals in avoiding further use of cocaine. As a first step in evaluating a medication to treat cocaine-use disorders in humans, its safety during combined dosing with cocaine and potential pharmacokinetic interactions with cocaine or cocaine metabolites must be assessed. To enhance the safety of human participants, interaction studies should be completed at each dose level before advancing to a higher dose. Otherwise, human subjects might be exposed to an adverse effect that was more intense because of the higher dose administered. At least for the 5 mg daily dose of donepezil, results of the present study do not show adverse cardiovascular effects or unfavorable pharmacokinetic interactions.

Cocaine is hydrolyzed by BuChE in the blood and hepatic carboxylesterase 2 to ecgonine methyl ester, and by hepatic carboxylesterase 1 to benzoylecgonine.^{25,26} If donepezil treatment had significantly inhibited BuChE or hepatic carboxylesterase 2 in the present study, greater and more prolonged plasma concentrations of cocaine with decreased levels of ecgonine methyl ester would be expected, or increased cocaine and decreased benzoylecgonine from inhibition of hepatic carboxylesterase 1. Because it is the most selective of marketed cholinesterase inhibitors, with 100-fold greater selectivity for inhibition of AChE over BuChE,²⁷ donepezil is presumably the least likely to augment tissue levels of cocaine through inhibition of BuChE. Results of the present study support this hypothesis. The effect of donepezil on hepatic carboxylesterases has not been reported, but lack of changes in plasma concentrations of ecgonine methyl ester or benzoylecgonine suggest any effect on these esterases is limited. The absence of these effects in experienced cocaine users receiving intravenous cocaine argue against significant enzyme inhibition after treatment with 5 mg daily of donepezil. Nonetheless, greater doses of cocaine with use over a more prolonged periods are likely in a non-laboratory setting.

Through increased availability of acetylcholine, cholinesterase inhibition can reduce heart rate by direct cardiac actions at the sinoatrial node, and increase blood pressure through activation of central type 1 and 2 muscarinic receptors.²⁸ Donepezil overdose in one patient produced bradycardia with systolic hypertension, which responded to treatment with atropine.²⁹ Hypertension was reported in 5% of Alzheimer disease patients who received donepezil.³⁰ Even so, other studies of clinically approved doses of donepezil reported neither decreases in heart rate nor increases in blood pressure.³¹ Consistent with this, we did not observe significant changes in either heart rate or blood pressure in the present study, prior to administration of cocaine.

Given the high potential for relapse to use of cocaine, treatment of cocaine-dependent patients with cholinesterase inhibitors requires a careful evaluation of the potential for negative interactions. Cocaine-induced lethality in rats is decreased and increased by low and high doses of the cholinesterase inhibitor physostigmine, respectively.³² Negative effects on survival could be explained by increases in blood pressure when cholinesterase inhibitors are administered at high doses. As previously reported, the present study showed that acute dosing with cocaine causes dose-related increases in heart rate and blood pressure. Given the potential of cholinesterase inhibitors to cause hypertension in some instances, an additive interaction between donepezil and cocaine would have augmented cocaine-induced hypertension. Instead, we observed an opposite effect, with donepezil attenuating increases in blood pressure produced by low-dose cocaine.

By increasing heart rate and blood pressure, cocaine acutely elevates cardiac workload. These actions may contribute to cardiac ischemia and also jeopardize brain vessels at risk for stroke. Recently, donepezil treatment in a rat cardiac ischemia model was shown to prevent heart failure and improve survival following coronary artery ligation.³³ In this rat model of ischemic heart disease, donepezil decreased heart rate without affecting blood pressure, and is thought to have acted by facilitation of cholinergic mechanisms that oppose increases in sympathetic tone. This parallels positive effects of vagal stimulation in experimental models of cardiac ischemia.³⁴ Cholinergic activation may also attenuate actions of cocaine that lead to ischemic events in the heart and brain. Although we did not record sympathetic function, future studies of cocaine interactions with cholinesterase inhibitors should consider this approach. Rather than potentiating cardiovascular events, administration of cocaine with cholinesterase inhibitors may be protective by ameliorating increases in sympathetic tone. This mechanism may explain attenuation of drug-induced increases in blood pressure caused by low-dose cocaine in the current study.

There are significant limitations of our study design. Because it is highly protein bound with an elimination half-life of 73.5 hours,³⁵ treatment with multiple donepezil doses does not achieve steady state plasma concentrations until 10 or more days of dosing. Although the three days of dosing utilized did not accomplish steady-state concentrations, our study design was a tradeoff between the length of confinement through hospitalization and its cost. Donepezil can acutely attenuate cocaine self-administration in rodent studies,¹⁶ and our aim was therefore to evaluate effects of subacute dosing in humans. Because of its potential toxicity, doses of cocaine were chosen to be the minimum that produced reliable subjective effects in a laboratory. Amounts of cocaine used in a non-research setting may be

significantly greater. Nonetheless, the higher cocaine dose chosen for the present study is similar to those typically used for human laboratory studies of cocaine. Significant dose-limiting effects of cocaine have been observed after higher doses in this setting.³⁶ In a number of instances, we found that cocaine and its metabolite concentrations were not detectable at latter time points. This reflects both individual differences in drug metabolism and the limits of detection by mass spectrophotometry.

Although further study is needed, pretreatment with the cholinesterase inhibitor donepezil does not augment cocaine bioavailability after exposure to the cocaine dose typically used in a laboratory setting. Rather than potentiating cocaine-induced increases in blood pressure, donepezil attenuated systolic blood pressure elevation following a low dose of cocaine. Diastolic blood pressure and heart rate were unaffected. Future studies should evaluate higher doses of donepezil for both the potential to decrease the reinforcing effects of cocaine and as a means of diminishing negative cardiovascular consequences.

Acknowledgments

This study was supported by grant R21-DA029787 issued to KG by the National Institutes of Health, Institute on Drug Abuse, Bethesda, MD 20892-9581; and grant 589-KG-0012 issued to KG by the Medical Research Service, Department of Veterans Affairs, Washington, DC, 20420.

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Figure 1.

Time-course of systolic blood pressure following intravenous injections of placebo or cocaine. Vertical axes show absolute change from baseline recorded in 12 participants at different time points. Group means and standard error are shown after treatment with intravenous placebo, low-dose cocaine (0.18 mg/kg), or high-dose cocaine (0.36 mg/kg, Panels C, B, and A respectively). Cocaine produced dose-related increases in systolic blood pressure, which were attenuated in donepezil-treated participants receiving low-dose cocaine. * indicates significant differences between treatment with donepezil and oral placebo by simple main effect, corresponding to $p < 0.001$.

Figure 2.

Peak values for cardiovascular measures following intravenous injections of cocaine.

Vertical axes show group means for maximum values of heart rate, diastolic blood pressure, and systolic blood pressure for 12 participants. When collapsed across oral treatment, high- but not low- dose cocaine produced significant elevations in all three measures. * indicates significant differences compared to intravenous placebo, with one and two symbols corresponding to $p < 0.026$ and $p < 0.01$ respectively.

Figure 3.

Plasma concentrations of cocaine and major metabolites following oral donepezil. Group means are shown for individual subjects with detectable levels (see text for details). Panel A: benzoyllecgonine, Panel B: cocaine, and Panel C: ecgonine methyl ester. Twelve participants received an initial injection of 0.18 mg/kg of cocaine 2 hours prior to time zero, with a second intravenous injection of 0.36 mg/kg at time zero. Concentrations of cocaine and metabolites were only determined after the second injection of cocaine. For pooled oral treatments, * indicates significant differences compared to baseline concentrations, $p < 0.01$. No significant effects of cholinesterase inhibition were observed.

Table 1

Cardiovascular measures after pretreatment with oral placebo or donepezil, prior to intravenous injections. Data shows group means in 12 subjects after receiving three days of either treatment, with standard error.

Measure	Placebo	Donepezil
Heart Rate (beats per minute)	78.8 (2.8)	73.7 (2.9)
Systolic Blood Pressure (mm Hg)	111.8 (2.7)	115.8 (3.2)
Diastolic Blood Pressure (mm Hg)	73.5 (1.7)	73.5 (1.9)

Table 2

Pharmacokinetic measures in subjects receiving oral placebo or donepezil. Non-compartmental analysis was used to derive measures from each individual subject, with mean values and standard error shown. Abbreviations include AUC for area under the plasma concentration versus time curve, AUMC for area under the first moment curve, CL for total body clearance, C_{max} for maximum concentration, MRT for mean residence time, VSS for apparent volume of distribution at steady-state, and t_{1/2} half-life.

Measure	Cocaine		Benzoylcegonine		Ecgonine Methyl Ester	
	Placebo	Donepezil	Placebo	Donepezil	Placebo	Donepezil
C _{max} (mg/L)	929 (257)	804 (181)	253 (16)	241 (16)	28.2 (4.4)	29.9 (2.1)
T _{max} (min)	10.0 (0.0)	10.0 (0.0)	117 (23.3)	131 (20.6)	64.6 (18.9)	65.5 (21.6)
AUC (mg*min/L)	34,503 (3,599)	40,812 (5,244)	111,454 (35,059)	130,509 (29,918)	14,804 (5,121)	11,443 (2,579)
AUMC (mg*min ² /L)	2,609,080 (335,256)	6,517,388 (3,239,674)	126,839,587 (64,525,678)	97,941,436 (29,827,602)	21,433,787 (14,328,239)	6,673,994 (2,444,112)
CL (ml/min)	1.050 (0.165)	0.867 (0.115)	0.525 (0.100)	0.449 (0.060)	4.04 (0.623)	4.47 (0.485)
MRT (min)	77.3 (6.4)	122.3 (34.6)	512 (174)	483 (106)	617 (203)	366 (94)
VSS (ml)	85.6 (15.7)	87.9 (13.3)	0.174 (0.040)	0.184 (0.032)	1.74 (0.32)	1.45 (0.30)
t _{1/2} (min)	59.1 (4.0)	91.3 (23.9)	349 (122)	324 (72)	426 (141)	251 (63)