Enadoline and Butorphanol: Evaluation of \( \kappa \)-Agonists on Cocaine Pharmacodynamics and Cocaine Self-Administration in Humans

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ABSTRACT

Preclinical studies have demonstrated that \( \kappa \)-opioid agonists can attenuate the neurochemical and behavioral effects of cocaine that are related to its reinforcing efficacy, suggesting that \( \kappa \)-agonists may serve as pharmacotherapies for cocaine dependence. This 8-week inpatient study examined the ability of enadoline, a selective and high-efficacy \( \kappa \)-agonist, and butorphanol, a mixed agonist with intermediate efficacy at both \( \mu \)- and \( \kappa \)-receptors, to reduce the direct pharmacodynamic effects and self-administration of intravenous cocaine in humans (\( n = 8 \)). Acute doses of intramuscular enadoline (20, 40, and 80 \( \mu G/kg \)), butorphanol (1.5, 3, and 6 mg/70 kg) and placebo were examined separately as pretreatments during each of three test sessions with cocaine in a constrained random order. A cocaine dose-effect session (0, 20, and 40 mg cocaine i.v., 1 h apart) examined direct pharmacodynamic interactions on subjective and physiological indices; self-administration sessions examined choice behavior for cocaine (40 mg i.v. for six trials) versus money 1) in the presence of a sample cocaine dose with money choices presented in ascending value, and 2) in the absence of a sample dose with money choices presented in descending values. Enadoline (80 \( \mu G/70 \) kg) significantly (\( p < 0.05 \)) reduced some of the positive subjective effects of cocaine (e.g., ratings of “high”), while butorphanol failed to modify subjective responses. Both agents were safely tolerated in combination with cocaine without adverse physiological responses. Cocaine self-administration was significantly greater across all pretreatment conditions when the sample dose was given and ascending money choices were used. Enadoline and butorphanol failed to modify cocaine self-administration. These data suggest that these \( \kappa \)-agonists may be safely administered in the presence of cocaine but do not produce significant attenuation of cocaine’s direct effects or self-administration under these acute dosing conditions.

Clinical pharmacology studies directed toward the development of treatments for cocaine dependence have cast a wide net to explore potential therapies from diverse pharmacological classes. These have been predicated largely on in vivo and in vitro preclinical data. A burgeoning literature on functional interactions between the \( \kappa \)-opioid receptor system and central dopamine systems intimately involved in the mediation of cocaine’s action suggests that \( \kappa \)-receptors are a rational target for cocaine medications development. Preclinical neurochemical studies have reported that \( \kappa \)-opioid receptor binding sites (Unterwald et al., 1994) and dynorphin concentrations (Sivam, 1989; Smiley et al., 1990) are significantly increased in primary striatal and limbic dopamine regions after chronic exposure to cocaine. Similarly, dynorphin mRNA and \( \kappa \)-receptor binding (Hurd and Herkenham, 1993; Staley et al., 1997) are increased in post-mortem studies of brain obtained from human cocaine abusers. Acute exposure to \( \kappa \)-agonists inhibits both dopamine release (Di Chiara and Imperato, 1988) and neuronal firing of dopamine neurons (Walker et al., 1987), while repeated exposure to \( \kappa \)-agonists reduces cocaine-induced expression of early gene mRNA (Steiner and Gerfen, 1995) and D2 receptors (Izenwasser et al., 1998). These data suggest a bidirectional interaction between central \( \kappa \)- and dopamine neurotransmitter systems.

Behavioral studies have demonstrated that pretreatment with \( \kappa \)-opioid agonists can attenuate the effects of cocaine, particularly as they relate to its reinforcing efficacy or abuse liability (for review, see Mello and Negus, 2000). \( \kappa \)-Agonists significantly decrease cocaine self-administration in rodents.

ABBREVIATIONS: ARCI, addiction research center inventory; PCAG, phenobarbital-chlorpromazine-alcohol group; LSD, lysergic acid diethylamide; ANOVA, analysis of variance.

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(Glick et al., 1995; Kuzmin et al., 1997) and monkeys (Negus et al., 1997; Mello and Negus, 1998). Moreover, k-agonists can attenuate cocaine-induced reinstatement of cocaine self-administration (Schenk et al., 1999), decrease the strength of a cocaine-induced conditioned place preference (Suzuki et al., 1992) and attenuate the discriminative stimulus effects of cocaine (Spealman and Bergman, 1992). Finally, studies have shown that repeated treatment with k-agonists can attenuate some responses to chronic cocaine administration, including the development of sensitization to its locomotor-activating and conditioned reinforcing effects (Heidbreder et al., 1993; Shippenberg et al., 1996).

These findings suggest that a selective k-opioid receptor agonist may attenuate the euphoric action of cocaine and thus have potential as a cocaine pharmacotherapy. The availability of the k-opioid receptor agonist enadoline (CI-977) allows this hypothesis to be tested in humans. Enadoline, an arylacetamide structurally similar to other arylacetamide k-agonists, including U50-488 and U69-593, is a potent compound that displays a high degree of selectivity for k-receptors (Boyle et al., 1990). It produces pharmacodynamic effects typical of k-opioids, including antinoceception in preclinical models, sedation, and diuresis, as well as a subjective-effect profile in humans characterized by dizziness, euphoria/dysphoria, drunkenness, and sensory distortions (Hunter et al., 1990; Reece et al., 1994).

As a prelude to the present study, we evaluated the safety and pharmacodynamic profile of enadoline over a range of acute doses from 10 to 160 µg/70 kg in humans with polysubstance abuse histories (Walsh et al., 2001). Doses up to 80 µg/70 kg were safe and tolerated well, although higher doses produced adverse psychiatric effects, including hallucinations and profound dysphoria. In that study, butorphanol was included for comparison and was evaluated over a wide range of doses. Butorphanol is a mixed opioid agonist/antagonist that has been widely administered to humans (Jasinski et al., 1976; Heel et al., 1978). Butorphanol, thought to act as both a partial k- and partial µ-opioid agonist (Leander, 1983; Dykstra, 1990; Vivian et al., 1999), produces an acute subjective effects profile comprised of both prototypic µ- and k-opioid effects (Jasinski et al., 1976; Preston and Bigelow, 1994; Walsh et al., 2001).

The primary aim of this study was to examine the acute pharmacological interaction of enadoline and butorphanol with cocaine over a range of doses and experimental procedures. The ability of enadoline and butorphanol to modify acute physiological and subjective responses to cocaine was examined using a placebo-controlled dose-effect interaction design. It was predicted that enadoline would reduce the subjective responses to cocaine administration related to its abuse liability, including measures of cocaine high and liking for cocaine. It is unknown clinically whether attenuation or antagonism of cocaine’s effects may lead to a decrease or an increase in cocaine use. Thus, the efficacy of enadoline and butorphanol to alter cocaine self-administration was also examined here using a novel adaptation of self-administration methodology used in preclinical and clinical laboratories. This self-administration procedure explored cocaine-taking behavior using two variations of a standard choice procedure following acute treatments with the selective k-opioid enadoline, or the mixed µ-k-opioid agonist butorphanol. In the first variation, a cocaine sample dose was administered prior to the initiation of the choice sessions, and subsequent choices for cocaine were made against varying amounts of money that began at low values. This arrangement was designed to engender higher rates of cocaine taking due to the potential “priming” by the sample dose and the low initial alternative reinforcers. The second set of parameters tested cocaine self-administration in the absence of a sample dose (i.e., no priming effect) with high initial money alternatives. This arrangement was designed to engender lower rates of cocaine taking and served as a model for relapse to cocaine use.

Materials and Methods

Participants

Participants (n = 12) were recruited through local newspaper advertisements. The study was approved by the Johns Hopkins Bayview Medical Center Institutional Review Board, written consent was obtained from each subject prior to participation, and subjects were paid for their participation. Exclusion criteria included any history of seizures, cardiovascular disorders, diabetes, any current condition requiring medication, abnormal laboratory values judged clinically significant, and any clinically significant psychiatric history. All participants were determined to be in good health by physical examination, an electrocardiogram, laboratory tests, medical history, and they were without significant psychiatric disturbance other than their drug abuse according to a structured psychiatric interview (Structured Clinical Interview for DSM-IV; First et al., 1996). Participants were required to have current cocaine and opiate use as evidenced by urinalysis tests and self-report. Participants were not physically dependent on opioids at the time of enrollment as determined by self-report as well as objective evidence, including residential observation while drug-free and at least one urine test negative for opiates during the recruiting and intake process.

General Procedures

Participants resided on a closed 14-bed residential research facility for approximately 7.5 weeks while participating. The unit is staffed by licensed nursing personnel 24 h/day and is used exclusively for behavioral pharmacology research. Recreational activities, exercise equipment, arts and crafts projects, reading materials, television, and video games were available. Urine specimens were collected daily and tested for illicit drugs on a random schedule at approximately weekly intervals. Testing was done on-site using an Enzyme Multiplied Immunoassay Technique Toxicology System (Behring Diagnostics, San Jose, CA) and/or by thin-layer chromatography to ensure the absence of drugs other than those administered experimentally. For the same purpose, alcohol breathalyzer tests also were given on admission and at weekly intervals. No illicit drug or alcohol use was detected during the study. Participants were maintained on a caffeine-free diet throughout their stay on the residential unit. Participants were allowed to smoke cigarettes ad libitum throughout their residential stay, except for 1 h before and throughout experimental sessions. Volunteers were required to refrain from eating for 1.5 h prior to the first scheduled drug administrations.

Study Design

The study used a double-blind, constrained-randomization, within-subject crossover design to explore the effects of acute doses of enadoline and butorphanol on response to intravenous cocaine and cocaine self-administration. Seven intramuscular pretreatment conditions were examined, each during a 1-week period, and included enadoline (20, 40, and 80 µg/70 kg), butorphanol (1.5, 3, and 6 mg/70 kg), and placebo. Each 1-week assessment consisted of three experimental sessions: one cocaine dose-effect interaction session and two...
cocaína se administrations (see description below). Sessions were conducted at least 48 h apart. For safety purposes, the first three subjects were exposed to the endadoline dose conditions in ascending order; this constraint was superimposed on an otherwise randomized dose schedule. After the safety of all dose combinations was established, the remaining five subjects were exposed to the seven pretreatment conditions in completely randomized order.

Drugs

Butorphanol tartrate (Apothecon, Princeton, NJ) and cocaína hydrochloride (Mallinkrodt, Inc., St. Louis, MO) were obtained from commercial sources. Endadoline hydrochloride was obtained as a gift from Parke-Davis (Ann Arbor, MI) and administered under an investigator-obtained Investigational New Drug application from the Food and Drug Administration (IND no. 52,410). All drugs were aseptically prepared under a horizontal laminar flow hood by filtering the solution through a 0.22-mm Millex-GS Millipore filter (Millipore, Bedford, MA) into a sterile, pyrogen-free vial (Lyoiphled, division of Fujisawa USA, Inc., Deerfield, IL).

Butorphanol doses were prepared from a commercial stock solution (Stadol 2 mg/ml) by diluting to the correct volume with saline. Endadoline, obtained as a powder, was weighed and dissolved in saline by diluting to the correct volume with saline. Cocaine powder was obtained from Parke-Davis (Ann Arbor, MI) and administered under an investigator-obtained Investigational New Drug application from the Food and Drug Administration (IND no. 52,410). All drugs were aseptically prepared under a horizontal laminar flow hood by filtering the solution through a 0.22-mm Millex-GS Millipore filter (Millipore, Bedford, MA) into a sterile, pyrogen-free vial (Lyoiphled, division of Fujisawa USA, Inc., Deerfield, IL).

Experimental Sessions

General Session Procedures. Experimental sessions took place in an isolated testing room designed to provide a consistent level of lighting, heat, sound, and visual stimuli. The subject was seated in a comfortable chair throughout the session in front of a personal computer (Apple IIGS; Apple Computer, Cupertino, CA), which recorded subjective and physiological responses. The research assistant remained seated behind the computer, initiated the data collection, monitored the subject, and provided observer ratings. A slow drip i.v. line remained in place throughout each session. A physician monitored the ECG continuously for 15 min following each injection. The criteria for aborting an intravenous cocaine challenge session after intravenous cocaine included abnormal ECG, systolic blood pressure >180 mm Hg, diastolic blood pressure >120 mm Hg, or heart rate >170 beats/min, or [(220-subjects age) × 0.85] for 4 or more consecutive min.

Cocaine Dose-Effect Sessions. Cocaine dose-effect sessions took place on Monday from 12:30 PM to 4:30 PM. Baseline data were collected for 30 min prior to the assigned intramuscular pretreatment injection. Thirty minutes after that double-blind i.m. injection, cocaine (0, 20, and 40 mg, in ascending order) was administered at 1-h intervals via the indwelling catheter. An array of physiological, subject-, and observer-rated measures was collected for 1 h after each i.v. injection as described below and outlined in Table 1.

Cocaine Self-Administration Sessions. These sessions took place on Wednesday (~12:30–3:30 PM) and Friday (~12:30–3:00). During each session, baseline data were collected for 30 min prior to the assigned intramuscular pretreatment injection. On Wednesdays, sessions were conducted that are hereafter referred to as the cessation self-administration sessions. In these sessions, a sample dose of cocaine (40 mg i.v.) was administered 30 min after the intramuscular pretreatment. Subjects were instructed that additional doses identical to the sample dose would be available later in the session during the choice trials. They were also instructed that the same dose would be available to them during the subsequent Friday session. Thirty

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>Collection schedule of dependent measures during the experimental sessions</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Time</td>
</tr>
<tr>
<td>Pretreatment period (all sessions)*</td>
<td>min</td>
</tr>
<tr>
<td>Enadoline, butorphanol, or placebo (i.m.)</td>
<td>-45</td>
</tr>
<tr>
<td></td>
<td>-30</td>
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<td></td>
<td>-25</td>
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<tr>
<td></td>
<td>-15</td>
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<tr>
<td></td>
<td>-5</td>
</tr>
<tr>
<td>Cocaine dose-effect sessions only (Monday)</td>
<td></td>
</tr>
<tr>
<td>Cocaine (0, 20, and 40 mg i.v.)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>0–14</td>
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<tr>
<td></td>
<td>10</td>
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<td></td>
<td>30</td>
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<tr>
<td></td>
<td>45</td>
</tr>
<tr>
<td>Cessation cocaine self-administration sessions only (Wednesday)**</td>
<td></td>
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<tr>
<td>Cocaine sample (40 mg i.v.)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>0–4</td>
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<tr>
<td></td>
<td>5</td>
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<td></td>
<td>10</td>
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<tr>
<td></td>
<td>15</td>
</tr>
<tr>
<td>Cessation and relapse self-administration sessions (Wednesday and Friday)</td>
<td></td>
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<tr>
<td>Six choice trials: cocaine versus money</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>0–4</td>
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<td>10</td>
</tr>
</tbody>
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* On-line measures for heart rate, blood pressure, oxygen saturation, and skin temperature were collected throughout all experimental sessions.
** Time 0 represents the start of each 15-min trial.
*** Administered only if cocaine was chosen over money.
minutes after the sample dose, the first of six consecutive trials began in which the subject had the opportunity to choose between receiving 40 mg of cocaine or a specified amount of money. The available money choice was $1, $4, $7, $10, $13, and $16 for the first through sixth trials, respectively. The intertrial interval was 15 min; initiation of the next trial was delayed if cardiovascular parameters exceeded safety criteria for receiving the next dose. On Fridays, sessions were conducted that are hereafter referred to as the relapse self-administration sessions. The design of these sessions was similar to the cessation self-administration sessions with three exceptions: 1) no sample dose was administered, hence the subjects initiated their choice behavior in a state of abstinence, 2) the first trial was initiated 30 min after the i.m. pretreatment, and 3) the order of the available money choices was reversed so that $16 was available during the first trial and the values declined across successive choice trials.

### Subject- and Observer-Rated Measures

Subject-rated measures included visual analog scales, the Addiction Research Center Inventory (ARCI) short form (Martin et al., 1971), subject- and observer-rated adjective checklists, and a street value rating. These were all collected according to the schedule outlined in Table 1. Subjects responded using a joystick to select the most appropriate response on the computer screen. The visual analog questions included “Do you feel any drug effect?, How high are you?, Does the drug have any good effects?, How much do you like the drug?, How much do you desire cocaine?, Does the drug make you feel drowsy or tired?, and Are you seeing or hearing things?”. The subjects responded by positioning an arrow along a 100-point line labeled with “none” at one end and “extremely” at the other. For the visual analog measures collected minute by minute after each intravenous infusion, subjects were instructed to rate the infusion they just received. The ARCI short form presented 49 true/false questions that are subdivided in scales sensitive to euphoria (morphine-benzodrine group), sedation (phenobarbital-chlorpromazine-alcohol group; PCAG), dysphoria (lysergic acid diethylamide; LSD), and amphetamine-like effects (benzodrine group and amphetamine).

The adjective checklist consisted of 16 items that the subjects rated from 0 (indicating “not at all”) to 4 (indicating “extremely”). The adjectives included excited, fearful, irritable, jittery, nervous, stomach upset/nausea, suspicious, skin itchy, sweating, nodding, drunken, tingling, energetic, floating/spaced out, confused, and light-headed. The observer-rated adjective scales, rated similarly to the subject-rated items, included the following: excited, irritable, jittery, skin itchy, sweating, nodding, drunken, and floating/spaced out. The subjects were asked to estimate the street value of the injection with, “How much would you pay for this injection?”, 15 min after each i.v. injection during the dose-effect evaluations and at 15 min after the i.m. injection during the self-administration sessions.

### Physiological Measures

Physiological measures, including respiratory rate, arterial oxygen saturation, skin temperature, systolic and diastolic blood pressures, and heart rate were monitored throughout all sessions. Respiratory rate was recorded every 5 or 15 min by an observer who counted the number of breaths taken by the subject for a 15-s period (Table 1). Oxygen saturation, skin temperature, systolic and diastolic blood pressure, and heart rate were collected by use of an automatic physiological monitoring device (Noninvasive Patient Monitor model 506; Criticare Systems, Waukeasha, WI) that was interfaced with the Macintosh computer. Heart rate, blood pressure, oxygen saturation, and skin temperature were collected every minute. Pupil diameter was determined from photographs taken in constant room lighting with a Polaroid camera (Polaroid Corp., Cambridge, MA) using a 2-fold magnification. Pupil photographs were collected according to the schedule outlined in Table 1.

### Statistical Analyses

All measures collected from the cocaine-dose effect sessions were analyzed initially as raw time course data by three-factor analysis of variance (ANOVA) for repeated measures (drug pretreatment condition × cocaine dose × time). The on-line physiological measures were first summarized across bins of individual minutes to yield a mean value for the following: 1) baseline prior to any drug administration, 2) baseline approximately 30 min after the intramuscular drug administration but prior to the first intravenous infusion, and 3) every 15-min interval after intravenous saline and cocaine administration.

To determine the direct action of the pretreatment doses of enandoline and butorphanol alone, all physiological, subjective, and observer-rated measures corresponding to approximately 30-min postintramuscular drug administration were analyzed by within-subject single factor ANOVA. Post hoc comparisons were made between the active pretreatment drug conditions and placebo. To determine the interaction between the α-agonists with cocaine, for most measures, the raw time course data were analyzed by use of three-factor ANOVA for repeated measures (pretreatment condition × cocaine dose × time). In these analyses, both baseline time points (preintramuscular and preintravenous injections) were excluded. The visual analog data were further analyzed as area-under-curve values using two-factor ANOVA (pretreatment condition × cocaine dose). Time course data for subjective and observer adjective ratings were transformed to change-from-baseline values prior to the ANOVA because of prominent baseline differences between the i.m. treatment conditions.

The self-administration data were analyzed by two-factor (pretreatment condition × test session [cessation versus relapse]) with-in-subject ANOVA. Outcomes examined included the total amount of money chosen during the session, number of cocaine injections obtained and the first amount of money chosen. For all statistical analyses, significant main and interaction effects were further evaluated by use of post hoc tests, including ANOVA and/or Tukey tests where appropriate. All repeated measures data were adjusted for sphericity using Huynh-Feldt corrections. Statistical significance was indicated when p ≤ 0.05.

### Results

#### Subjects

Twelve volunteers were enrolled and eight completed the study. Of the four who failed to complete, one obtained full-time employment soon after admission and left to take a job, one was diagnosed as human immunodeficiency virus-positive during screening and left to pursue treatment, and the other two exceeded the cardiovascular safety criteria following cocaine administration and were discharged. The remaining eight participants, whose average age was 38.5 years, were all males (two Caucasian, six African-American) and reported sporadic use of both heroin and cocaine; they were not seeking treatment for their drug abuse. Subjects reported using cocaine an average of 15 of the last 30 days with an average history of 15 years of cocaine use; they all met diagnostic criteria for cocaine dependence. They reported using heroin an average of 10.3 of the last 30 days with an average history of 10.4 years of use. Five of eight subjects met criteria for opiate abuse according to the criteria of the Diagnostic and Statistical Manual-Version IV. For these five subjects, their reported heroin use averaged 12.2 of the last 30 days. The remaining three subjects reported heroin use an average of seven of the last 30 days. Four subjects met criteria for alcohol abuse and three for cannabis abuse. None met diagnostic criteria for current abuse or dependence of sedative/hypnotics, other stimulants, or hallucinogens. All
subjects smoked cigarettes but were not physically dependent on any other psychoactive drugs at the time of their participation.

Direct Effects of Enadoline and Butorphanol

The direct effects of enadoline and butorphanol alone are described here first because their presence or absence impacted the subsequent data analyses used to evaluate the interactions of these agents with cocaine. Direct effects were assessed by examining the data obtained after the intramuscular injection but preceding the first infusion from the cocaine dose-effect sessions. These data reflect the activity of the pretreatment agents at the time of the first cocaine challenge, but, because they emanate from the first 30-min postinjection, they do not necessarily reflect the peak response to butorphanol or enadoline. Figure 1 illustrates the dose-effect functions for four outcome measures (see figure legend for statistical outcomes). Both drugs produced significant increases on a variety of subjective-effect measures compared with placebo. As can be seen in the upper panels of Fig. 1, enadoline and butorphanol produced significant and dose-dependent increases in global ratings of “any drug effect”; the magnitude of these effects covered a comparable range of scores for both drugs. Butorphanol produced significant increases in ratings of “high” (Fig. 1) and good effects \( [F(6,42) = 3.01; p < 0.05; \text{data not shown}] \), while enadoline did not. Conversely, enadoline, but not butorphanol, increased ratings on the LSD scale of the ARCI \( [F(6,42) = 4.3; p = 0.004; \text{Tukey test}; p < 0.05] \). No other scales of the ARCI were altered.

The observer-rated adjective scales revealed significant main effects for drug condition on four of eight measures. Ratings of “drunken” \( [F(6,42) = 4.45; p = 0.033] \) and “floating/spaced out” \( (F = 6.7; p = 0.006) \) were significantly increased by the highest doses of enadoline and butorphanol (Tukey test; \( p < 0.05 \)). While significant main effects of drug were obtained on the measures of “nodding” \( (F = 5.6; p = 0.005) \) and “skin itchy” \( (F = 3.9; p < 0.05) \), these were due to butorphanol, but not enadoline. A similar dissociation between enadoline and butorphanol was evident on physiological measures. Butorphanol altered typical opioid agonist measures by decreasing pupil diameter \( (F = 3.38; p = 0.023) \), while increasing skin temperature \( (F = 3.25; p = 0.013) \), while increasing skin temperature (Fig. 1). Enadoline did not significantly modify any of the physiological measures.

![Graph](https://via.placeholder.com/150)

Fig. 1. Data shown are mean responses \((n = 8; \pm 1 \text{ S.E.M.})\) on four outcome measures assessing the direct effects of intramuscular enadoline and butorphanol. Scores were obtained approximately 30-min postintramuscular injection (i.e., preceding the first i.v. challenge). Significant main effects of drug condition were found for the visual analog measures (top) of “Do you feel any drug effect?” \( [F(6,42) = 4.15; p = 0.003] \) and “How high are you?” \( (F = 3.41; p < 0.05) \) and for the physiological measures (bottom) of pupil diameter \( (F = 30.4; p < 0.001) \) and skin temperature \( (F = 3.25; p = 0.013) \). Filled symbols denote significant differences from the placebo condition based upon Tukey \( t \) tests \((p < 0.05)\). Vertical bars represent \( \pm 1 \) standard error of the mean.
Pharmacological Interaction: Cocaine Dose-Effect Evaluation

Interactions with Cocaine: Subjective and Observer-Rated Measures. Visual analog scales. Cocaine alone produced significant increases in ratings of “good effects”, “high” (Fig. 2; see figure legends for primary statistical outcomes), “drug effect”, and “liking” (data not shown). The pattern of responding was largely similar across the four measures. Cocaine produced dose-related increases in scores after pretreatment with i.m. placebo. Butorphanol pretreatment failed to alter the response to cocaine regardless of dose. In contrast, enadoline at all doses tended to decrease the response to cocaine, particularly the higher challenge dose of cocaine (i.e., 40 mg). However, this attenuation by enadoline reached statistical significance only after administration of the highest enadoline pretreatment dose (80 µg/70 kg; Tukey test; \( p < 0.05 \)). Inspection of the time course data reveal that the suppression of scores after enadoline appears as a reduction across the whole curve rather than a change in the time to onset or the time to peak response. There were no significant main effects of pretreatment condition or cocaine injection on the visual analog measures of “bad effects”, “desire for cocaine”, “drowsy/tired”, or “seeing/hearing things”.

ARCI. Scores for the LSD (dysphoria) scale are shown in Fig. 2 (bottom left). Cocaine significantly increased ratings on the LSD scale (see figure legend for statistical outcomes). Enadoline at 80 µg elevated LSD ratings alone (see placebo cocaine data) and this eliminated the dose-effects of cocaine on this measure, while butorphanol produced additive effects. The PCAG scale (sedation) also showed a significant main effect of cocaine, whereby cocaine tended to decrease PCAG ratings (Fig. 2). The highest doses of enadoline (80 µg/70 kg) and butorphanol (6 mg/70 kg) alone significantly increased PCAG ratings thereby blocking the cocaine dose-effects. Results from the Sedation scale were similar to the profile obtained with the PCAG scale \( F(6,42) = 6.74; p < 0.0001 \). Cocaine produced significant increases on the Benzedrine scale \( F(6,42) = 3.66; p = 0.019 \); these were lowered after the highest dose of both enadoline and butorphanol. There were no significant effects on the morphine-benzedrine group, amphetamine, or euphoria scale.

Subject- and observer-rated adjectives. Although subjects were instructed to respond to these rating scales with respect to the intravenous infusion rather the intramuscular injection at all time points after the first infusion, in the case of the subject- and, particularly, the observer-rated adjective...
scales, scores did vary as a function of pretreatment condition. Therefore, the analyses of the adjective ratings scales were adjusted for baseline effects (i.e., change-from-baseline scores). Because the analyses were complex, with many outcomes (three main factors plus all possible interactions), only the most relevant factors, that is, the direct effects of cocaine (i.e., main effect of cocaine) and their modification by the pretreatment agents (i.e., cocaine × pretreatment drug interactions) will be reported here. Cocaine alone produced significant increases on the subject ratings of “excited”, “jittery”, and “energetic” ($p < 0.05$). Significant interactions between the pretreatment drug and cocaine were found for ratings of “sweating”, “nodding”, “tingling”, “floating/spaced out”. These interactions were generally characterized by the presence of these symptoms after pretreatment with butorphanol or enadoline and their reversal by treatment with active cocaine. In other words, these drug/drug interactions were largely due to cocaine modifying the prominent actions of the $\kappa$-agonists rather than butorphanol or enadoline modifying cocaine’s action. Similar findings were noted on the observer-ratings of “nodding” and “floating/spaced out” ($df = 12, 84; p < 0.05$).

**Street value questionnaire.** Cocaine produced significant and dose-dependent increases on dollar ratings of street value [$F(2,14) = 18.6; p < 0.001$]; neither butorphanol nor enadoline significantly altered these ratings.

**Interactions with Cocaine: Physiological Measures.** Cocaine alone produced significant effects on heart rate, systolic and diastolic blood pressure, skin temperature, and oxygen saturation as evidenced by statistically significant main effects for the cocaine injection factor ($p < 0.05$). Illustrative time course data are shown for two measures, heart rate and pupil diameter, in Fig. 3. The direct effects of cocaine alone are displayed within the i.m. placebo pretreatment data. As can be seen, a transient rise in heart rate occurred immediately after the saline infusion (0-mg condition). Both active doses of cocaine (20 and 40 mg) produced significant elevations in heart rate that peaked at approximately 10 min after the infusion and declined thereafter. Both enadoline and butorphanol modestly, but significantly,

![Fig. 3](https://example.com/fig3.png)

**Fig. 3.** Data shown are the mean ($n = 8$) values obtained in response to cocaine challenge (shown along the x-axis) for heart rate (top) and pupil diameter (bottom). These time course data were obtained after pretreatment with enadoline (left column) and butorphanol (right column). Scores are the raw values for heart rate (beats per minute) and pupil diameter (in millimeters). The baseline value (BL) was obtained prior to intramuscular pretreatment. Time $-30$ represents the data obtained 30 min after i.m. treatment with enadoline or butorphanol (i.e., prior to the i.v. injection of saline at time 0), and reflects the direct effects of the intramuscular pretreatment. These two time points are shown for illustrative purposes and are not included in the statistical analysis of cocaine effects. The time course analyses revealed a significant main effect of cocaine injection for heart rate [$F(2,14) = 11.8; p = 0.003$], and a significant main effect for both cocaine injection [$F(2,14) = 35.2; p < 0.0001$] and pretreatment condition [$F(6,42) = 44; p < 0.0001$] on pupil diameter. Filled symbols represent significant differences compared with the placebo condition at the same time point (Tukey; $p < 0.05$).
reduced the tachycardic response to cocaine, in part, by exerting their own modest direct effects on heart rate (Tukey test; \( p < 0.05 \); 80 \( \mu \)g of enadoline versus 0 mg and 6 mg of butorphanol versus 0 mg). However, there were no statistically significant interactions between cocaine and enadoline or butorphanol. Cocaine alone produced significant dose-dependent increases of systolic \( F(2,14) = 22.4; p < 0.001 \) and diastolic blood pressure \( F(2,14) = 25.6; p = 0.001 \), and neither enadoline nor butorphanol altered the pressor action of cocaine in any discernible manner (data not shown).

As shown in Fig. 3 (bottom), cocaine alone produced significant and transient increases in pupil diameter. These effects were unaltered by enadoline. However, butorphanol administration alone produced miosis that was dose-dependent (see −30 time point) and of long duration. While the dose-dependent mydriatic effects of cocaine are still evident in the presence of butorphanol, the curves are shifted downward proportionate with the degree of miosis produced by butorphanol. Similar to the profile for pupil diameter, cocaine alone significantly decreased skin temperature \( F(2,14) = 32.9; p < 0.001 \), while butorphanol, but not enadoline, significantly increased skin temperature thus attenuating the overall effect of cocaine \( F(6,42) = 5.8; p < 0.001 \); Tukey test, \( p < 0.05 \). There were also significant pharmacological effects on the measure of oxygen saturation that were characterized by cocaine producing modest, but significant \( F(2,14) = 6.1; p = 0.024 \), increases in oxygen saturation, and butorphanol, but not enadoline, producing proportionate and dose-dependent decreases in this measure [data not shown; \( F(6,42) = 2.99; p = 0.037 \)].

**Cocaine Self-Administration**

**Self-Administration after Placebo Pretreatment.** The data shown in Fig. 4 depict only the self-administration choice behavior when intramuscular placebo served as the pretreatment agent. The upper panels illustrate the number of subjects (of eight) choosing cocaine at each dollar choice trial during the cessation (left) and relapse (right) self-administration procedures. Under the cessation procedure, when a sample dose was given and the initial alternative dollar choice was low, all subjects chose cocaine (40 mg) over the two lowest valued money reinforcers ($1 and $4). Fewer subjects chose cocaine on all subsequent higher dollar choice trials ($7–16). Overall, more subjects chose cocaine than money for all choice trials in the cessation procedure. In contrast, under the relapse procedure, when no sample cocaine dose was given and the initial alternative reinforcer value was high ($16), only two of eight subjects chose cocaine over money. The number of subjects choosing cocaine increased with successively decreasing alternative reinforcer values. Related data, showing the average amount of dollars chosen across subjects as a function of trial, are shown in the

![Fig. 4. Results from the two cocaine self-administration procedures, cessation (left) and relapse (right), collected following pretreatment with placebo are shown. The top graphs illustrate the total number of subjects (y-axis) of eight who chose cocaine (40 mg i.v.) over the alternative reinforcer (on the x-axis shown in dollars) for each of six consecutive trials. The bottom graphs illustrate the average (n = 8 subjects) amount of money chosen (y-axis) during each trial as a function of the amount of money available during that trial (x-axis).](image-url)
lower panels of Fig. 4. The average amount of money chosen is not a perfect mirror of the cocaine choice data (as would be the actual number of money choices), because the subjects were allowed to choose between cocaine and money choices independently across trials. These data show that, under the cessation self-administration procedure, subjects’ choices were not related in an orderly manner to the value of the alternative reinforcer, in contrast to the orderly data obtained in the relapse procedure. Moreover, the mean total amount of money chosen in the cessation session was less than half that chosen in the relapse session (average across trials: cessation = $13.625 and relapse = $29.88).

**Self-Administration after Enadoline and Butorphanol Pretreatment.** Data shown in Fig. 5 illustrate the effects of enadoline and butorphanol pretreatment on cocaine choice in both the cessation and the relapse procedures. The upper panels illustrate the results following enadoline administration. In the cessation procedure, following placebo pretreatment, subjects chose an average of 4.75 cocaine injections per session. Pretreatment with enadoline at 20, 40, and 80 μg did not significantly alter choice behavior. In the relapse procedure, subjects chose approximately 3.5 of six injections of cocaine after placebo pretreatment. The number of cocaine choices increased compared with placebo after pretreatment with all active doses of enadoline; however, this trend failed to reach statistical significance in the post hoc analyses. Data shown in the lower panels illustrate the effects of butorphanol pretreatment on cocaine choice behavior in the two paradigms. Butorphanol did not significantly alter the number of cocaine choices in the cessation self-administration procedure although, on average, the number of cocaine choices was modestly lower under each of the active butorphanol conditions compared with placebo. In the relapse procedure, butorphanol failed to alter cocaine self-administration under any condition.

When the self-administration data were collapsed over all of the pretreatment conditions, there was a significant difference between the cessation and relapse self-administration procedures with respect to the number of cocaine versus money choices made. Significant differences between the procedures were obtained for the total money chosen during session \(F(1,7) = 7.2; p = 0.031\) and the number of cocaine injections chosen \(F(1,7) = 7.4; p = 0.03\), whereby more cocaine, and less money, was chosen in the cessation procedure than the relapse procedure regardless of the pretreatment condition. In addition, there was a significant difference between the two procedures when the initial amount of money chosen over cocaine was examined \(F(1,7) = 24.5; p = 0.002\). Examination of the individual subject data reveal that this difference in cocaine-taking between the two procedures occurred in all subjects, except for one who took cocaine on almost all occasions (82 of 84 trials) regardless of the experimental manipulation.

**Discussion**

The findings from this study reveal that acute doses of butorphanol and enadoline can be safely tolerated when given in combination with cocaine over a range of doses but provide little evidence of clinically meaningful therapeutic interactions between these \(\kappa\)-agonists and cocaine on behavioral outcomes. While numerous significant interactions on physiological measures were noted, due largely to the differing direct effect profiles of the \(\kappa\)-opioids compared with cocaine, enadoline produced only modest decreases on only a small subset of subjective responses to cocaine related to its...
abuse liability, while butorphanol failed to modify any. Both butorphanol and enadoline failed to significantly alter cocaine self-administration when examined under an array of behavioral and pharmacological conditions.

The pharmacodynamic interaction data suggest that acute enadoline modestly reduced some of the positive subjective effects of cocaine (e.g., ratings of “high” and “liking”), although this was observed for only some measures and only after treatment with the highest dose of enadoline. Butorphanol failed to modify any of the subjective responses to cocaine despite the wide range of test doses and the evident pharmacological activity of butorphanol. These data suggest that neither enadoline nor butorphanol substantially modify the subjective response to cocaine to the degree that may be required for clinical impact on cocaine use under these acute dosing conditions. These findings are not inconsistent with preclinical drug discrimination studies from which mixed dosing conditions. These findings are not inconsistent with preclinical drug discrimination studies from which mixed results have been obtained, whereby κ-agonists produce variable or no alteration in the discriminative stimulus effects of cocaine (Spealman and Bergman, 1992; Woolfolk and Holtzman, 1997; Negus and Mello, 1999). The primary finding of importance with respect to the physiological interactions between cocaine and butorphanol or enadoline was the relative safety of these drugs in combination. All of the acute dose combinations were tolerated without adverse effects and, importantly, there was no evidence of synergistic effects that could pose significant safety risks. Indeed, both enadoline and butorphanol actually dampened the tachycardic response to cocaine. Although there was a number of other notable physiological interactions between cocaine and butorphanol, these were primarily the result of the two drugs producing direct effects in the opposite direction (e.g., butorphanol producing miosis and cocaine producing mydriasis) and probably have little therapeutic significance.

This represents the first evaluation of the self-administration procedures used herein, thus comment on the behavior observed under control conditions (i.e., the placebo pretreatment) is warranted to provide a fuller context for the discussion of the pharmacological outcome data. In the present study, reliable differences in the rate of cocaine self-administration were observed between the two experimental procedures, despite the fact that the dose of cocaine (40 mg) and the number of cocaine choice trials were held constant between the two conditions. Cocaine intake was significantly greater in the cessation procedure (in which a sample dose was given just prior to the start of the choice phase and the initial value of the alternative reinforcer was low) compared with the relapse procedure (in which no sample dose was given and the initial alternative reinforcer value was high). The difference in cocaine intake between the two procedures was also apparent under the active κ-agonist pretreatment conditions. This was, in fact, the initial aim of testing the two parametric arrangements: to achieve differential rates of cocaine self-administration. Although self-administration of cocaine in human laboratory models is generally dose-dependent (Foltin and Fischman, 1992; Hatsukami et al., 1994), subjects tend to choose all or most of the cocaine available regardless of the experimental conditions when the available cocaine dose is at the upper end of the test range and approximates those used illicitly (e.g., i.v. doses greater than 30 mg). For example, a review of earlier human self-administration studies reveals that cocaine is chosen on 85% or more of the available trials when the i.v. dose is greater than 30 mg (Fischman et al., 1990; Foltin and Fischman, 1997, 1998). In the present cessation procedure, cocaine was chosen on approximately 80% of the occasions under placebo pretreatment conditions consistent with these earlier studies. In contrast, the relapse procedure engendered cocaine choices on fewer than 60% of the opportunities under the placebo control condition. From a methodological perspective, this may be an important finding for experimental models used to evaluate putative cocaine medications. It has been difficult to assess the sensitivity and validity of the human laboratory models in the absence of any effective treatments (i.e., the required positive control condition). It has long been known that one important factor influencing the effects of drug treatments on behavioral outcomes is the baseline rate of that behavior (Dews, 1958). The present method may provide an opportunity to examine the effects of putative medications on cocaine self-administration under conditions whereby different rates of intake can be produced within the same individual. This may be particularly useful when examining agents that have only partial efficacy (e.g., one that is effective against lower but not higher cocaine doses) or differentiating between medications useful for suppressing ongoing cocaine use versus those helpful in preventing relapse to use.

Because two experimental factors were varied simultaneously across the cessation and relapse procedures (i.e., sample dose and alternative reinforcer value order), it is impossible to disentangle their relative contributions to the observed outcome. The administration of a sample dose prior to the initiation of choice trials (cessation procedure) is a common feature among the majority of previous human cocaine self-administration studies (Fischman et al., 1990; Foltin and Fischman, 1992). It is possible that the sample dose actually acts as a stimulus to increase or prime more cocaine-taking. Preclinical studies have shown that self-administration can be increased and/or reinstated after a period of abstinence by a single experimenter-administered dose of drug (for review, see Carroll and Comer, 1996). This phenomenon, known as priming, occurs for several drug classes, including cocaine (Spealman et al., 1999). In the present study, it is possible that either the sample dose in the cessation procedure or the first self-administered dose, as subjects were more likely to choose cocaine early in the session versus a low-value alternative reinforcer, served as a priming dose to stimulate more cocaine-taking. Virtually no empirical data are available on the occurrence of priming in humans, however, the importance of both drug-related stimuli (e.g., paraphernalia, drug environments) and drug stimuli (i.e., the initial lapse to drug use) are widely accepted as critical factors contributing to relapse and ongoing drug use. Despite the strengths of the present methodology, this study also has some weaknesses that need to be explored more fully in subsequent studies. The order of presentation of relapse and cessation sessions was not counterbalanced and there was no placebo sample or “priming” injection given during the cessation sessions to assess the potential role of conditioning. Moreover, only a single dose of cocaine was used here due to the large number of pretreatment conditions assessed and it is unknown whether the interaction with enadoline or butorphanol would differ with other doses of cocaine. Finally, all of the subjects were opiate-experienced, although not physically dependent, and thus their response to the pretreatment...
agents may have been influenced by tolerance and, therefore, might differ from that of an opiate-naïve population.

Acute doses of both enadoline and butorphanol failed to alter cocaine administration under either the cessation or relapse procedures in this study. These findings are in contrast to those obtained in most preclinical self-administration studies showing that κ-opioid agonists as a class (Glick et al., 1995; Kuzmin et al., 1997; Negus et al., 1997; Mello and Negus, 1998), and enadoline (Mello and Negus, 1998) and butorphanol (Mello et al., 1993), specifically, can significantly reduce cocaine self-administration. Negative outcomes have been obtained, however, suggesting that the efficacy of the κ-opioid agonists to reduce cocaine self-administration may be dependent upon the dose of cocaine (Mello and Negus, 1998) and whether acquisition or ongoing self-administration behavior is examined. It is important to note that in the present study all of the pretreatments were administered as acute doses rather than as chronic pretreatments. Although acute dosing studies are an important step in the evaluation of the safety of drug interactions, it is possible that outcomes following chronic treatment may differ than those obtained after acute administration and that pharmacotherapies are typically administered on a chronic basis when used in a clinical setting. While numerous methodological differences may account, in part, for the discrepancy between the preclinical results and present clinical outcome, these data do not suggest that enadoline or butorphanol can substantially modify the effects of cocaine when administered under acute dosing conditions. It is also possible that other dosing differences may account for the observed outcome. Although it is difficult to compare studies accurately across species with respect to doses without careful interspecies scaling, the weight-adjusted doses of enadoline and butorphanol used in the present study do overlap with the range of doses shown to decrease cocaine self-administration significantly in preclinical studies. Because preclinical studies have found that κ-opioid agonists commonly suppress cocaine self-administration at doses that suppress other behaviors (i.e., they are not necessarily selective for cocaine), it is possible that the doses required to suppress cocaine self-administration in humans would be intolerable because of adverse side effects (Walsh et al., 2001). In the present study, there was a nonsignificant trend for the highest dose of enadoline to increase cocaine self-administration in the relapse procedure; this was also the only dose of enadoline that significantly reduced the positive subjective effects of cocaine in the pharmacodynamic interaction evaluation. This observation is interesting because numerous preclinical studies have shown that partial antagonism of cocaine can lead to increased cocaine self-administration (Woolverton and Kleven, 1988). Although this trend failed to reach significance, the data support the speculation that an antagonist approach to cocaine medication development could actually lead to an increase, rather than a decrease, in cocaine use. This scenario would arise clinically if partial blockade of cocaine’s effects simply led to a compensatory increase in cocaine taking to surmount the blockade.

In conclusion, this study provides important safety data regarding the interaction of κ-opioid agonists and cocaine in humans. Cocaine was tolerated well when administered alone and in combination with enadoline or butorphanol over a range of doses. Enadoline did produce some attenuation of cocaine’s subjective effects, but this occurred only at the highest dose and the magnitude of the effect was modest. In contrast to the minimal interactions on subjective measures, a number of significant physiological interactions between cocaine and the κ-opioid pretreatments were observed, but most were not of clinical significance. Using two sets of parameters in this novel choice self-administration paradigm yielded reliably different rates of cocaine self-administration, and this procedure may be useful for future evaluations of potential pharmacotherapies. Despite numerous preclinical studies reporting that an array of κ-opioid agonists can reduce the reinforcing effects of cocaine in the self-administration paradigm as well as other models, neither enadoline nor butorphanol significantly altered cocaine self-administration over a range of conditions in this study. These data do not provide evidence of clinically meaningful interactions for these κ-opioid agonists with cocaine under acute dosing conditions. However, the present study does provide the requisite safety information to proceed with evaluations of chronic κ-opioid administration for the treatment of cocaine abuse and dependence.

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