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Effects of prototypic calcium channel blockers in methadone-maintained humans responding under a naloxone discrimination procedure^a

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Abstract

Accumulating evidence suggests that L-type calcium channel blockers (CCBs) attenuate the expression of opioid withdrawal and the dihydropyridine L-type CCB isradipine has been shown to block the behavioral effects of naloxone in opioid-maintained humans. This study determined whether two prototypic L-type CCBs with differing chemical structures, the benzothiazepine diltiazem and the phenylalkamine verapamil, attenuate the behavioral effects of naloxone in methadone-maintained humans trained to distinguish between low-dose naloxone (0.15 mg/70 kg, i.m.) and placebo under an instructed novel-response drug discrimination procedure. Once discrimination was acquired, diltiazem (0, 30, 60, 120 mg) and verapamil (0, 30, 60, 120 mg), alone and combined with the training dose of naloxone, were tested. Diltiazem alone produced 33–50% naloxone- and novel-appropriate responding at 30 and 60 mg and essentially placebo-appropriate responding at 120 mg. Verapamil alone produced 20–40% naloxone- and 0% novel-appropriate responding. Diltiazem at 60 mg decreased several ratings associated with positive mood and increased VAS ratings of “Bad Drug Effects” relative to placebo, whereas verapamil increased ratings associated with euphoria. When administered with naloxone, diltiazem produced 94–100% naloxone-appropriate-responding with 6% novel-appropriate responding at 60 mg (n=3). When administered with naloxone, verapamil produced 60–80% naloxone- and 0% novel-appropriate responding (n=5). Diltiazem decreased diastolic blood pressure and heart rate whereas verapamil decreased ratings of arousal relative to placebo. These results suggest that CCBs with

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different chemical structures can be differentiated behaviorally, and that diltiazem and verapamil do not attenuate the discriminative stimulus effects of naloxone in humans at the doses tested.

Keywords

opioid withdrawal; naloxone; humans opioid dependence; drug discrimination; calcium channel blockers

1. Introduction

Opioid dependence continues to be a serious public health problem, particularly with the dramatic rise in prescription opioid abuse (Substance Abuse and Mental Health Services Administration, 2010). Traditional methods of opioid detoxification, including tapering off methadone and supportive treatment of symptomatology with alpha2-adrenergic receptor agonists, are limited by the high relapse rate and lack of efficacy in relieving subjective symptoms (Amato et al., 2005; Gowing et al., 2002; Jasinski et al., 1985; Rounsaville et al., 1985). Although buprenorphine (BUP) appears to relieve withdrawal symptoms similarly to methadone and may resolve these symptoms faster than methadone, withdrawal symptoms (Gowing et al., 2009) and opioid craving (Sanders et al., 2012) are still moderate and highly variable among patients (Kleber, 2007a; Kleber, 2007b). Meanwhile, prescribing opioid analgesics to non-cancer patients with chronic pain has resulted in withdrawal symptoms after stopping the medication (Cowan et al., 2003). The number of adolescents and young adults using opiates is also increasing and chronic opioid maintenance treatment is undesirable in this population (Stotts et al., 2009). Thus, this study seeks to improve current treatments for opioid withdrawal, including opioid detoxification strategies and smoothing the transition from methadone maintenance to BUP or naltrexone maintenance, by examining the effects of novel agents; that is, calcium channel blockers, on the expression of naloxone-precipitated withdrawal in opioid-dependent humans.

The expression of opioid withdrawal appears to be mediated not only through mu opioid and noradrenergic systems (Koob and Weiss, 1992; Nestler, 1992; Redmond and Krystal, 1984), but also secondary mechanisms involving excitatory amino acids (e.g., (Akaoka and Aston-Jones, 1991; Rasmussen and Aghajanian, 1989; Tokuyama et al., 1996). NMDA receptor antagonists decrease the severity of naloxone-precipitated withdrawal in opiate dependent rats (Koyuncuoglu et al., 1990; Rasmussen et al., 1991). Moreover, partial agonists or antagonists at the strychnine-insensitive glycine modulatory site have been shown to attenuate opioid antagonist-precipitated withdrawal in nonhumans (Belozertseva et al., 2000; Bristow et al., 1997; Kosten et al., 1995; Popik et al., 1998). NMDA receptor activation is also associated with increased intracellular calcium levels, with calcium channel blockers attenuating precipitated opiate withdrawal (Baeyens et al., 1987; Bongianini et al., 1986; Ramkumar and El-Fakahany, 1988; Seth et al., 2011).

We have previously shown that the opioid agonist hydromorphone blocked the effects of naloxone in opioid-maintained volunteers responding under a naloxone discrimination procedure (Oliveto et al., 1998a). The relative efficacy of non-opioid agents to attenuate the effects of naloxone was: calcium channel blocker isradipine > A2A receptor agonist clonidine partial glycine agonist D-cycloserine >>> NMDA glutamate antagonist dextromethorphan (Oliveto et al., 2003a; Oliveto et al., 2004; Oliveto et al., 2003b). These findings demonstrate the utility of this human model of opiate withdrawal for examining both opioid and nonopioid mechanisms underlying its expression and suggest that calcium channel blockers may be good pharmacological targets for treating withdrawal. This study examined further the impact of calcium channel blockers on withdrawal by determining the

effects of two prototypic L-type calcium channel blockers with different chemical structures, the phenylalkamine verapamil and the benzothiazepine diltiazem, on response to naloxone under the novel-response discrimination paradigm.

2. Materials and methods

2.1 Subjects

Six female and five male opioid dependent volunteers (aged 27–53 years) were recruited from the Center for Addiction Treatment and Rehabilitation Clinic and the UAMS Substance Abuse Treatment Center. Each subject gave written informed consent to participate in the study. Participants had to meet the following criteria: between the ages of 18–65; maintained on a stable dose of methadone (+ or – 10 mg) for at least 1 month prior to study entry; in “good standing” in the methadone maintenance program in order to participate (i.e., compliance with scheduled medication and group therapy session h, defined as < 3 missed methadone medications and missed < 3 group or <3 individual therapy sessions in the two months prior to study participation); urine sample negative for illicit drugs prior to study entry; able to read and understand English; adequate birth control practices; not pregnant; no plans to become pregnant; liver function tests less than 3 times normal; BUN, creatinine and thyroid function tests within normal range; no unstable medical condition or stable medical condition that would interact with study medications or participation; no current diagnosis of other drug or alcohol physical dependence (other than tobacco); no history of major psychiatric disorder (psychosis, schizophrenia, bipolar, depression); no current or recent use of any over-the-counter psychoactive drug, prescription psychoactive drug or any drug that would have major interaction with drugs to be tested; no history of severe reaction to Narcan challenge; and no EKG abnormalities, such as bradycardia (<60 bpm), prolonged QTc interval (>425 ms), Wolff-Parkinson White syndrome, wide complex tachycardia, 2nd degree, Mobitz type II heart block, 3rd degree heart block, or left or right bundle branch block. Eligibility was ascertained through a comprehensive evaluation that included complete physical, neurological, and clinical psychiatric examinations, routine laboratory studies, and an electrocardiogram. Subjects were paid hourly wages depending on the phase of the experiment they were in, such that they received US\$5/h during the training phase, US\$6/h during the test of acquisition phase, and US\$7/h during the testing phase. During each session the subject could also earn a bonus of up to US\$20 depending on their performance. This protocol was approved by the University of Arkansas for Medical Sciences Institutional Review Board.

Ten subjects were Caucasian and one was African American. Subjects reported being in good standing in a current opioid agonist treatment program for a mean of 19.4 ± 8.4 months (range: 3–101 months), verified by research staff. Nine subjects were regular tobacco users. Participants reported using alcohol (2/12) and benzodiazepines (1/12) at least once during the three months prior to the study entry. Participants weighed a mean of 88.5 kg (range= 58.0–124.3 kg) at study entry.

2.2 Setting

This study was conducted in a quiet room either at the Center for Clinical Research located in the John L. McClellan Memorial Veterans Hospital or in the Outpatient Behavioral Pharmacology Laboratory at the University of Arkansas for Medical Sciences (UAMS). The laboratory consisted of a six-station experimental room with an adjacent lounge where subjects could relax after the experimental portion of the session while waiting for drug effects to subside. A research nurse administered all medications and was present for the entire session. A physician was available by pager during each session.

2.3 Experimental Procedure

Subjects were trained to discriminate naloxone (0.15 mg/70 kg) from placebo (vehicle) under an instructed novel-response (i.e. active dose, placebo dose, 'novel') discrimination procedure (Bickel et al., 1993; Kamien et al., 1994; Oliveto et al., 1994, 1998). An orientation session in which drug was not administered was used to familiarize the subjects with the procedures. The study then proceeded in three phases:

2.3.1 Training (Phase 1)—Subjects were administered naloxone (0.15 mg/70 kg) and placebo each twice in randomized order and *were informed* of the drug's letter code (e.g. Drug A or Drug B) at the time of drug administration. Subjects were never informed of the actual identities of the drugs, but were given a list of drugs that they might receive during the course of the study. Letter codes associated with the training drug stimuli were varied across subjects.

2.3.2 Tests-of-acquisition (Phase 2)—To ensure that subjects learned to discriminate between the naloxone training dose and the placebo vehicle, the drug letter code associated with the drug administration *was not revealed* until the end of the experimental session. Subjects had to meet an accuracy criterion of 80% correct responding on four consecutive sessions in order to enter the testing phase. If this criterion was not met within 10 sessions, subjects were dismissed from the study.

2.3.3 Training (Phase 3)—Dose-effect curves for diltiazem (0, 30, 60, and 120 mg, orally) and verapamil (0, 30, 60, and 120 mg, orally) alone and in combination with the training dose of naloxone (0.15 mg/70kg) were obtained. Due to a pharmacy error, one participant was given naloxone at 0.2 mg/70kg during all test-of-acquisition and test sessions that occurred during the third phase, except for one session in which diltiazem at 60 mg was co-administered. After each session was completed, subjects were informed only that it was a test day and that the drug code would not be revealed. During this phase, subjects were informed that if they received a drug not precisely like either of the training conditions, only novel-appropriate responses would be reinforced (see Bickel et al., 1993); however, in actuality, subjects' bonus earnings during all test sessions were equal to the average earned on the preceding four test-of-acquisition sessions; that is, earnings were not contingent upon discriminative performance.

Test-of-acquisition sessions (i.e. administration of the training dose of naloxone or placebo) were interspersed among the test sessions to ensure that the training conditions still appropriately controlled responding. If the training drug stimuli failed to control the appropriate response in one of these test-of-acquisition sessions, two more test-of-acquisition sessions were conducted. If the training drug stimuli did not control the appropriate response in two sessions additional test-of-acquisition sessions were added until the criterion for acquisition of the discrimination (i.e. four consecutive correct) was met again. The ratio of test to test-of-acquisition sessions was approximately 1:2.

2.3.4 Experimental session—Sessions were conducted 3–5 days/week, depending on subject and staff availability, and typically began between 0800–0900 h. The beginning of the experimental sessions remained consistent within subjects, who typically remained in the laboratory for approximately 5 h. A baseline field sobriety test was conducted at the beginning and end of each experimental session. Subjects were instructed to: (1) count backwards from 100 by a specified number; (2) touch the tip of their nose with their index finger with their eyes closed; (3) walk seven steps forwards and backwards 'from heel to toe'; (4) complete the digit symbol substitution test (DSST) on a computer; and (5) undergo an alcohol breathalyzer test. A pre-drug assessment cycle followed which consisted of

baseline self-report questionnaires (see below). Vital signs (blood pressure, heart rate, respiratory rate) were taken. Immediately afterward, one capsule was administered (–160 min) followed by a second capsule 90 min later (–70 min). Seventy min after the second capsule was given an injection was given to the upper arm or hip (0 min). Subjects completed tasks during two post-drug assessment cycles, conducted 20 and 40 min after the injection (Preston et al., 1987). Each assessment cycle lasted approximately 10 min and consisted of discrimination measures, self-reported drug effects and vital signs (see below). After the second post-injection assessment cycle was completed, a sealed envelope was opened for each subject, informing subject and experimenter of the letter code of the administered drug or that the session had been a test day. Subjects were then escorted to the adjacent room to recover from any drug effects. At this time, subjects were given food and were permitted to smoke either outside the building at the VA or in a special smoking room at UAMS. At the end of sessions in which a test drug was administered as well as at least one session in which each of the training conditions was administered, an ECG trace was taken before the subject was released from the lab to ensure that the QTc interval was less than 450 ms.

Subjects were instructed to abstain from caffeine and food for at least 4 h before each session and were required to smoke their last cigarette from their regular brand about 10 min before the baseline field sobriety tests. No smoking was permitted from this time until the end of the experimental session. Otherwise, subjects were instructed to maintain a regular pattern of smoking for the duration of the study. No food or beverage, except water, was allowed during the experimental session.

2.4 Dependent Measures

2.4.1 Discrimination measure—During each post-injection assessment, subjects were asked to distribute 50 points among the two drug codes and novel response option; depending on how certain they were of the identity of the drug administered. Only correct response during training or test-of-acquisition sessions were converted to monetary reinforcement for subjects. Subjects earned up to US\$20 per session for maximal correct responding, with each point distributed on the correct code being worth US\$0.20.

2.4.2 Self-report measures—Computerized assessments were created in LabView and administered via Macintosh PowerBooks. The assessments were programmed in such a way that 1) each subject had his/her own template of questionnaires that are prescheduled based on the timing of assessments, 2) each question must be answered in order to go to the next task or question, and 3) each answer has a “built in” range of appropriate values such that out-of-range answers will not be accepted. Assessments were the short version of the Addiction Research Center Inventory Short Form (ARCI), consisting of 49 true/false questions that are scored as five subscales: morphine-benzedrine group (MBG), a measure of “euphoria;” pentobarbital-chlorpromazine-alcohol group (PCAG), a measure of “sedation;” lysergic acid diethyl amide (LSD), a measure of “dysphoria;” and the benzedrine (BG) and amphetamine (A) scales, which are sensitive to amphetamine-like effects (Jasinski, 1977; Martin et al., 1971); an Adjective Rating Scale (ARS), listing 32 adjectives rated on a 5-point scale from 0 (not at all) to 4 (extremely) that were grouped into 3 subscales: 1) Agonist Scale, consisting of the adjectives *carefree, coasting or spaced out, drive, dry mouth, drunken, energetic, flushing, good mood, heavy or sluggish feeling, nodding, pleasant sick, relaxed, skin itchy, sleepy, sweating, talkative, tingling, and turning of stomach*; 2) Antagonist Scale, consisting of the adjectives *agitated, chills, gooseflesh, restless, runny nose, shaky, tired, and watery eyes*; and 3) Mixed Agonist/Antagonist Scale, consisting of the adjectives *confused, depressed, floating, headache, lightheaded, and numb* (Preston et al., 1987); Visual Analog Scales (VAS), consisting of eight 100-point visual-

analog scales anchored with “not at all” on one end and “extremely” on the other. On these scales subjects reported the extent to which they experienced the strength of the drug effect, drug-liking, “good” drug effects, “bad” drug effects, drug-induced “high,” and how similar to the code for naloxone, placebo or dissimilar to naloxone or placebo; Profile of Mood States (POMS), consisting of 72 adjectives that are scored on eight subscales: *anxiety*, *depression*, *anger*, *vigor*, *fatigue*, *confusion*, *friendliness*, and *elation* (McNair et al., 1981), and a Side-Effects Rating Scale (SER) that lists 15 adjectives describing possible side effects of test agents that are rated on a 5-point scale from 0 (not at all) to 4 (extremely), including dizzy, headache, lightheaded, flushed, dry mouth, drowsy, nauseous, stomach upset, sleepy, blurred vision, tired, muscle aches, tremor, sluggish, and confused. This allows for a summation of scores for an overall side effect score as well as an examination of specific symptom scores. At the end of the second post-drug assessment cycle, subjects also completed a pharmacological drug class questionnaire, in which they indicated which type of drug they thought they had received from the following list: placebo (blank or nothing), opiates (heroin, methadone, etc.), phenothiazines (Haldol, major tranquilizers), barbiturates and sleeping medications, antidepressants (desipramine, imipramine), opiate antagonists (naloxone, naltrexone), hallucinogens (marijuana, mushrooms, etc.), benzodiazepines (Xanax, Halcion, Valium, etc.), stimulants (cocaine, amphetamines, etc.), or phencyclidine (PCP, angel dust) (Preston et al., 1987).

2.4.3 Physiological measures—Heart rate, blood pressure, and respiratory rate were taken at −160, −70, 0, 20, 40, 60, 85, and 115 min. Heart rate and blood pressure were measured with a blood pressure cuff automated through a GE Dinamap Carescape V100 vital signs monitor (Med-Electronics, College Park, MD).

2.5 Drugs

Subjects were maintained on methadone hydrochloride at an average dose of 93.75 mg/day (range: 60–120 mg) by the opioid maintenance clinic they were attending. Subjects continued attending their respective opiate maintenance treatment facility during and after their participation in the study. The training dose of naloxone and naloxone placebo were administered via intramuscular injections (0.36–0.85 ml). Injection volumes remained consistent within individuals unless a subject’s weight changed by more than 5 lb (2.25 kg), in which case injection volumes were adjusted. Diltiazem and Verapamil were administered via blue opaque capsules. Drugs were prepared by the UAMS Research Pharmacy for naloxone hydrochloride (Hospira, Lake Forest, Illinois, USA), diltiazem hydrochloride (Teva, North Wales, Pennsylvania, USA), and verapamil hydrochloride (Mylan, Morgantown, West Virginia, USA). Naloxone placebo consisted of 0.9% NaCl. Diltiazem and verapamil placebos were made up of either cellulose microcrystalline powder or lactose. Naloxone was injected 20 min prior to the first post-drug assessment cycle (Preston et al., 1987). Diltiazem was administered 180 min prior to the first post-drug assessment cycle, because the peak affects of diltiazem occur at approximately 3–5 h post-administration (Bottiger et al., 2001). Verapamil was administered 90 min prior to the first post-drug assessment cycle, because the peak affects of verapamil occur at approximately 1–1.5 h post-administration (Hla et al., 1987; Sasaki et al., 1993). Each drug was administered in a double blind and “double-dummy” fashion.

The order of dose testing for each series of test compound dose effect curves was typically random, with two exceptions. First, when a naloxone-test compound dose-effect curve combination was administered for the first time, doses were tested in ascending order, such that if adverse effects increasingly occur, higher doses were not tested and the dose range of the test compound was adjusted accordingly. Second, the highest dose of test compound alone was always tested prior to in combination with naloxone. Dose-effect curve

determinations were counterbalanced across subjects. Test-of-acquisition sessions were interspersed throughout to ensure continued correct discrimination and provide further training.

2.6 Data Analyses

Discrimination data within each session were averaged across the two post-drug assessment cycles and reported as percentage of drug-appropriate responding. Results from the self-report and physiological measures are reported as the mean change from pre-drug scores.

During the testing phase, the significance of dose effects on discrimination, self-reports, and physiological measures were evaluated for diltiazem alone (0, 30, 60, 120 mg), the naloxone training dose alone and in combination with diltiazem (naloxone at 0.15 mg/70kg plus 0, 30, 60, 120 mg of diltiazem), verapamil alone (0, 30, 60, 120 mg), and the naloxone training dose alone and in combination with verapamil (naloxone at 0.15 mg/70kg plus 0, 30, 60, 120 mg of verapamil). Placebo data used in these analyses were the averaged data across all placebo sessions during testing. Naloxone training dose data used in the analyses described above were the averaged data across all naloxone training sessions during testing. Self-report and physiological data for each dose-effect curve determination were entered into repeated measures ANOVA, with dose and post-drug assessment cycle as factors. Discrimination data were entered into repeated measures ANOVA, with dose as the factor. In order to determine whether dose-related changes in a dependent measure occurred in a particular direction, polynomial regressions were used to determine if any main effect showed a linear-, quadratic- or cubic-shaped function. In cases where cubic-shaped function occurred, *post-hoc* comparisons were made between doses 0–30, doses 0–60, and doses 0–120. For all statistical analyses, a $P = 0.05$ was used to infer statistical significance and $0.05 < P < 0.1$ was used to indicate a trend. Analyses were performed using PROC GLM in SAS 9.2.

3. Results

3.1 Discrimination Performance During Training and Test of Acquisition and During Testing

Three of eleven subjects did not complete enough sessions to determine whether they met the criterion for discrimination (i.e., 80% correct drug code identification across four consecutive sessions). Reasons for discontinuing participation included disliking drug-effects ($n=1$), obtaining employment ($n=1$) and PI dismissal after having a greater than desired reaction to the test drug ($n=1$). Two participants could not meet the criterion for discrimination and did not continue into the third phase. Six participants met the discrimination criterion within a mean of 6.8 sessions (range: 4–9) and entered the test phase. Of these six participants, two were female, six were Caucasian and five were regular tobacco smokers. These subjects were maintained on an average methadone dose of 89.4 mg (range 60–120 mg).

Of the six participants who entered the test phase, five completed at least one set of dose-response curve determinations (i.e., test drug alone and combined with naloxone) and three completed the entire phase, such that three completed the entire diltiazem dose-response curve, one completed all but the 30 mg dose of diltiazem alone, and five completed the verapamil dose-response curve set. Reasons for early termination during this phase included disliking drug-effects ($n=2$) and obtaining employment ($n=1$).

3.2 Effects of Naloxone on Self-Report and Physiological Measures During Training and Test-of-Acquisition

Effects of the training dose of naloxone and placebo during training and test of acquisition are shown in Table 1. Naloxone produced significantly increased ratings on PCAG and LSD subscales of the ARCI and VAS ratings of “drug effect,” “bad effects,” and “like naloxone” relative to placebo. Conversely, placebo significantly increased VAS ratings of “good effects,” “liking,” and “like placebo” and ratings on the Opioid Agonist subscale of the AR relative to naloxone. Naloxone significantly increased ratings on the anxiety, depression, and anger subscales of the POMS and significantly decreased the POMS ratings for vigor, friendliness, elation, and positive mood relative to placebo. Systolic and diastolic blood pressure decreased following administration of placebo relative to naloxone.

On the pharmacological drug class questionnaire, placebo was identified primarily as “placebo” on 12 out of 19 occasions (63.2%), as well as “antidepressant” on 1 occasion (5.3%), “barbiturate” on 4 occasions (15.8%), “opiate antagonist” on 1 occasion (5.3%), and “opiates” on 1 occasion (5.3%). In contrast, the training dose of naloxone was identified primarily as “opiate antagonist” on 16 out of 20 occasions (80%), as well as “barbiturate” on 2 occasions (10%), “opiates” on 1 occasion (5%), and “placebo” on 2 occasions (10%).

3.3 Effects of Diltiazem Alone and Verapamil Alone

3.3.1 Discrimination Performance—The effects of diltiazem alone and verapamil alone on naloxone-appropriate responding under the drug discrimination task are shown in Fig. 1. Diltiazem alone produced no significant changes in naloxone-appropriate ($F(3,6)=1.85$, $P=0.24$) or ‘novel’-appropriate responding ($F(3,6)=1.12$, $P=0.41$) compared to placebo (Fig. 1, top left panel). Diltiazem did, however, produce a trend toward decreases in ‘placebo’-appropriate responding ($F(3,6)=7.94$, $P=0.07$). Verapamil alone did not alter naloxone-appropriate ($F(3,12)=0.77$, $P=0.53$), ‘novel’-appropriate ($F(3,12)=1.00$, $P=0.43$) or placebo-appropriate ($F(3,12)=0.57$, $P=0.64$) responding relative to placebo (Fig. 1, top right panel).

3.3.2 Self-Report and Physiological Measures—Fig. 2 and 3 show those measures in which a main effect of dose ($P \leq 0.05$) occurred for either diltiazem or verapamil alone. Diltiazem (left panels), but not verapamil (right panels), showed a significant cubic-shaped dose-related changes on Friendliness ($F=12.29$, $df=1$, $P=0.025$) and Positive Mood ($F=7.94$, $df=1$, $P=0.05$) subscales of the POMS (Fig. 2, top and middle panels) as well as the agonist subscale of the ARS ($F=54.41$, $df=1$, $P=0.002$; Fig. 2, bottom panels), such that ratings decreased at the 60 mg dose relative to placebo ($F=16.04$, $df=1$, $P=0.01$; $F=9.75$, $df=1$, $P=0.04$; $F=91.22$, $df=1$, $P=0.0007$; respectively).

Diltiazem, but not verapamil, produced significant dose-related changes ($P < 0.05$) in a cubic manner on VAS ratings of “bad effects” ($F=9.32$, $df=1$, $P=0.04$ Fig. 3, top panels), with higher ratings at 60 mg relative to placebo ($F=13.58$, $df=1$, $P=0.02$). Diltiazem, but not verapamil, also produced a linear increase in ratings on the LSD subscale of the ARCI ($F=33.08$, $df=1$, $P=0.005$, Fig. 3, middle panels), with scores higher at the 120 mg relative to placebo ($F=154.01$, $df=1$, $P=0.0002$). Conversely, verapamil, but not diltiazem, produced a linear, dose-related increase in scores on the MBG subscale of the ARCI ($F=23.09$, $df=1$, $P=0.001$; Fig. 3, bottom panels), with scores higher at the 120 mg dose relative to placebo ($F=8.05$, $df=1$, $P=0.02$). Neither agent alone significantly altered vital signs (data not shown).

Participants identified diltiazem as placebo, antidepressant or opioid antagonist (see table 2). Participants were more likely to identify diltiazem as placebo as the dose increased. At least

half of the participants identified verapamil as an active drug (i.e., opiate, barbiturate, antidepressant, opioid antagonist) at every dose.

3.4 Effects of Diltiazem or Verapamil in Combination with Naloxone

3.4.1 Discrimination Performance—The effects of diltiazem or verapamil in combination with the training dose of naloxone on naloxone-appropriate responding under the drug discrimination task are shown in Fig. 1. When combined with naloxone, diltiazem did not alter naloxone-induced naloxone- ($F(3,9)=2.52$, $P=0.12$), or novel-appropriate ($F(3,9)=1.00$, $P=0.44$) responding, but did significantly decrease placebo-appropriate responding ($F(3,9)=7.06$, $P=0.01$; Fig. 1, bottom left panel). Meanwhile, verapamil in combination with naloxone did not produce a significant change in naloxone- ($F(3,12)=0.56$, $P=0.65$), novel- ($F(3,12)=1.00$, $P=0.43$) or placebo- appropriate ($F(3,12)=0.58$, $P=0.64$) responding relative to naloxone alone (Fig. 1, bottom right panel).

3.4.2 Self-Report and Physiological Measures—Those measures showing a main effect of dose ($P \leq 0.05$) for either verapamil or diltiazem are shown in Fig. 4. Verapamil, but not diltiazem, in combination with the training dose of naloxone produced a significant quadratic-shaped dose related decrease in ratings on the arousal subscale of the POMS ($F=20.98$, $df=1$, $P=0.025$) relative to naloxone alone (Fig. 4, top right panel), with scores being lower at the 60 mg dose relative to placebo ($F=43.20$, $df=1$, $P=0.0002$). Diltiazem administered concomitantly with naloxone produced a significant, linear, dose-related decrease in diastolic blood pressure ($F=26.38$, $df=1$, $P=0.002$) relative to naloxone alone (Fig. 4, next to bottom left panel), with a lower reading at the 120 mg dose relative to placebo ($F=24.54$, $df=1$, $P=0.003$). When combined with naloxone, diltiazem produced a quadratic-shaped decrease in heart rate relative to naloxone alone ($F=32.20$, $df=1$, $P=0.001$; Fig. 4, bottom left panel), in that the 60 mg dose produced a lower reading relative to placebo ($F=44.64$, $df=1$, $P=0.0005$). Verapamil did not significantly alter diastolic blood pressure or heart rate (Fig. 4, middle and bottom right panels).

All participants consistently identified each diltiazem-naloxone combination as an opioid antagonist (Table 2). Similarly, the vast majority of participants identified verapamil at each dose as an opioid antagonist when administered concomitantly with naloxone.

4. Discussion

The results of this study show that diltiazem and verapamil produced few behavioral effects when given alone and generally did not alter naloxone-induced behavioral effects when administered concomitantly with naloxone in opioid-dependent humans responding under a naloxone discrimination procedure. That neither verapamil nor diltiazem attenuated the behavioral effects of naloxone was unexpected. These results are inconsistent with prior findings with diltiazem (Kishioka et al., 1996; Tokuyama and Ho, 1996) and verapamil (Blackburn-Munro et al., 2000) in nonhumans and our prior finding with isradipine in this paradigm (Oliveto et al., 2004). These findings do not appear to be due to recruiting a different opioid dependent population than accessed in our prior studies (Oliveto et al., 2003a; Oliveto et al., 2002; Oliveto et al., 1998b), in that the self-reported effects of naloxone appear to be similar to those reported previously (Oliveto et al., 2004; Oliveto et al., 2002; Oliveto et al., 1998b).

One reason for the discrepant findings may be due to the doses tested. Even though the highest acutely-administered dose tested for each calcium channel blocker was the highest initial recommended daily dose for the treatment of hypertension (Cardizem package insert, Biovail Laboratories International SRL, rev 11/09; Calan package insert, Pfizer, 10/11), it may have been too low to attenuate naloxone's effects, particularly given that blood pressure

and heart rate were not substantially affected by either drug when administered alone. However, each agent alone did alter at least one self-report measure and diltiazem decreased naloxone-induced increases in diastolic blood pressure, indicating that these drugs did have some behavioral activity at the doses tested. Moreover, diltiazem at an acute dose of 120 mg has been shown to decrease blood pressure and produce side effects such as headache and nausea in healthy nonsubstance users (Bottiger et al., 2001). In addition, isradipine produced few self-reported effects but effectively attenuated the discriminative stimulus and some self-reported effects of naloxone, even at a dose that did not lower blood pressure (Oliveto et al., 2004). Thus, although dosage may be a factor, it likely does not wholly account for the disparate results.

Another reason for the discrepancy may be the relatively small sample size, in that four and five participants completed the diltiazem-naloxone and verapamil-naloxone dose effect curves, respectively. However, sample sizes of 4–8 are typical for human drug discrimination studies (see (Kamien 1993; Kelly 2003)), likely due to the labor-intensive nature of these studies (Kelly 2003). The results of drug discrimination studies with humans have been shown to be similar to those with nonhumans, demonstrate pharmacological specificity and generally show a high concordance with self-reports (e.g., see reviews by Kamien et al., 1993; Preston and Bigelow, 1991; Schuster and Johanson, 1988; Kelly et al., 2003). Unfortunately, to our knowledge, no studies examining the effects of calcium channel blockers in opioid-treated nonhumans responding under an opioid antagonist discrimination procedure have been published. Thus, whether the lack of concordance between the present findings and the nonhuman data regarding diltiazem and verapamil is due to differences in methodology is unclear at this time.

Although both test drugs are calcium channel blockers, they produced differing profiles of behavioral effects when administered alone, with diltiazem producing effects that would be considered unpleasant whereas verapamil produced effects associated with euphoria. These differences may account for the appearance that diltiazem enhanced the effects of naloxone. In addition, these findings are in contrast to those with the dihydropyridine calcium channel blocker isradipine, which mainly produced decreases in VAS ratings of “like placebo” and blood pressure in our prior study (Oliveto et al., 2004). The somewhat differing behavioral profiles may be due to the different chemical structures and binding properties of these agents. These drugs bind to different sites at the L-type calcium channel to reduce the influx of extracellular calcium into the cell, with binding domains for dihydropyridines (Striessnig et al., 1991b) and benzothiazepines (Kurokawa et al., 1997) reportedly located on the extracellular membrane in myocytes and the binding site for phenylalkylamines (Striessnig et al., 1991a) located on the intracellular surface. For instance, in pentobarbital-anesthetized dogs, the dihydropyridine nifedipine and diltiazem dose-dependently reversed, whereas verapamil worsened methacholine-induced bronchoconstriction, suggesting that blockade of L-type calcium channels on the extracellular, but not intracellular, surface may attenuate this (Hirota et al., 2003). The dihydropyridine nifedipine has been shown to acutely increase muscle sympathetic nerve activity in microneurography studies (Noll et al., 1994), whereas verapamil may reduce activity in the sympathetic nervous system (Kailasam et al., 1995). Dihydropyridines are more likely to produce side effects related to vasodilatation (Opie, 1988), while verapamil produces constipation (e.g., (Rosei et al., 1997; White et al., 2001)). Verapamil and diltiazem tend to produce reductions in heart rate and AV conduction (Braunwald, 1982; Dougherty et al., 1992). Moreover, although there is some overlap in the indications for the prototypic drugs from each subtype, there are some indications unique to one or two subtypes, such as Raynaud’s Disease for nifedipine and verapamil and paroxysmal supraventricular reentry tachycardia for verapamil and diltiazem (e.g., see (Roland et al., 1998)), which may reflect their differing efficacies to alter particular cardiovascular effects (e.g., see (Hardman and Lunnon, 2001)). Although all

three agents have shown efficacy in attenuating opioid withdrawal-like effects in various nonhuman paradigms (e.g., (Alfaro et al., 1990; Barrios and Baeyens, 1991; Colado et al., 1993; Morrone et al., 1990)), the different binding properties of these agents may produce differences, however subtle, in not only the efficacy of these compounds to attenuate the behavioral effects of naloxone in humans, but also their side-effect profile in terms of, for example, cardiovascular effects. Their overall profile of effect therefore is necessary to determine their relative utility not only as a monotherapy, but also as an augmentation treatment strategy for opioid withdrawal. Indeed, nifedipine, but not verapamil or diltiazem, has been shown to inhibit migrating myoelectrical complexes of the small intestine in the morphine-naïve rats (Thollander et al., 1993).

To our knowledge, no clinical trials of diltiazem and only one uncontrolled clinical trial of verapamil (Shulman et al., 1998) for treating opioid withdrawal have been published. In this pilot inpatient study, verapamil at 40–80 mg three times daily did alleviate withdrawal symptoms and craving in opioid-dependent patients, many of which also underwent a methadone taper (Shulman et al., 1998). However, the efficacy of verapamil has not been confirmed in a randomized, placebo-controlled trial. Based on the results of the present study, verapamil or diltiazem may not be the most promising agents for alleviating opioid withdrawal, even given the preliminary findings with verapamil (Shulman et al., 1998). Overall, the results of this study suggest that calcium channel blockers can be differentiated based on their behavioral effects in humans under controlled laboratory conditions.

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Fig. 1.

The effects of diltiazem alone (top left panel) or verapamil alone (top right panel) and diltiazem (bottom left panel) or verapamil (bottom right panel) in combination with the naloxone training dose on discrimination performance under the point distribution task. Abscissa: dose of drug in mg. Ordinate: Percentage naloxone- (filled circles) or 'novel'- (open circles) appropriate responding. Each point in the diltiazem alone dose effect curve represents the mean across three participants. Each point in the diltiazem-naloxone dose effect curve represents the mean across four participants. Each point in the verapamil dose effect curves represents the mean across five participants. Each bar represents standard error of the mean. Points above "P" and "Nx" represent means of participants across placebo and naloxone training days, respectively, during the test phase.

Fig. 2.

The effects of diltiazem alone (left panels) or verapamil alone (right panels) on selected self-report measures. Abscissa: dose of drug in mg. Ordinate: Mean change from predrug. Each point in the diltiazem dose effect curve represents the mean across three participants. Each point in the verapamil dose effect curve represents the mean across five participants. Each bar represents standard error of the mean. Points above "P" represent means of participants across placebo training days during the test phase. Data points significantly different from placebo are indicated by an asterisk (*).

Fig. 3.

The effects of diltiazem alone (left panels) or verapamil alone (right panels) on selected self-report measures. Abscissa: dose of drug in mg. Ordinate: Mean score (top panels) or Mean change from predrug (middle and bottom panels). Each point in the diltiazem dose effect curve represents the mean across three participants. Each point in the verapamil dose effect curve represents the mean across five participants. Each bar represents standard error of the mean. Points above "P" represent means of participants across placebo training days during the test phase. Data points significantly different from placebo are indicated by an asterisk (*).

Fig. 4.

The effects of naloxone alone and in combination with increasing doses of diltiazem (left panels) or verapamil (right panels) on selected self-report and physiological measures. Abscissa: dose of drug in mg. Ordinate: Change from predrug. Each point represents the mean across four participants for diltiazem and five participants for verapamil. Each bar represents standard error of the mean. Points above “Nx” represent means of participants across naloxone training days during the test phase.

Table 1

Effect of the Training Dose of Naloxone (0.15 mg/70 kg i.m.) and Placebo on Self-Report Measures During Training and Test-of-Acquisition

Measure	Naloxone		Placebo		<i>p</i> ^a	
	<i>M</i>	<i>S.E.M.</i>	<i>M</i>	<i>S.E.M.</i>		
ARCI						
PCAG	4.41	1.77	1.08	0.69	51.75	0.002
LSD	4.85	1.83	0.54	0.69	13.01	0.02
MBG	-3.15	2.00	-1.87	1.15	0.85	<i>ns</i>
AMPH	-1.69	1.45	-0.87	0.89	0.47	<i>ns</i>
BG	-1.15	1.22	-0.73	1.03	0.003	<i>ns</i>
VAS						
drug effect	51.17	10.28	31.41	10.13	13.97	0.02
good effects	20.51	7.61	43.70	9.50	34.21	0.004
bad effects	59.49	11.73	25.05	7.91	55.60	0.002
high	23.07	8.41	19.35	7.79	1.84	<i>ns</i>
liking	21.95	7.95	40.65	8.96	18.74	0.01
"like naloxone"	79.07	11.97	24.70	15.10	84.07	0.0008
"like placebo"	14.44	9.89	73.92	15.24	1612	<0.0001
"like novel"	24.24	9.59	22.92	10.01	0.30	<i>ns</i>
Adjective ratings						
Agonist scale	-1.10	1.87	2.51	3.45	74.59	0.001
Antagonist scale	1.85	1.53	0.73	1.29	1.74	<i>ns</i>
Agonist/Antagonist scale	1.18	0.78	0.73	1.03	3.71	<i>ns</i>
POMS						
Anxiety	3.83	2.01	-0.94	0.85	35.63	0.004
Depression	2.20	1.75	-0.94	0.93	12.52	0.02
Anger	1.10	1.24	-0.11	0.53	14.93	0.02
Vigor	-5.10	2.26	-0.97	1.13	18.58	0.01
Fatigue	0.78	0.91	0.06	1.10	7.22	<i>ns</i>
Confusion	1.50	0.88	0.50	0.76	5.67	<i>ns</i>
Friendliness	-5.25	2.33	-0.31	1.88	38.85	0.003

Measure	Naloxone		Placebo		<i>p^a</i>
	<i>M</i>	<i>S.E.M.</i>	<i>M</i>	<i>S.E.M.</i>	
Elation	-2.90	1.36	-0.31	1.10	0.02
Arousal	-3.55	2.29	-2.47	1.54	<i>ns</i>
Positive mood	-5.1	2.38	0.64	1.14	0.004
Vitals					
Systolic Blood Pressure	0.12	13.96	-12.8	11.96	0.01
Diastolic Blood Pressure	0.31	8.59	-5.32	9.78	0.05
Heart Rate	-8.36	13.62	-12.82	6.01	<i>ns</i>

Note. Each value represents the mean $\pm$ *S.E.M.* change from predrug measures across 5 participants. Data were obtained from the four training and four test-of-acquisition sessions in which participants met criterion for acquisition of the discrimination. POMS=Profile of Mood Symptoms; ARCI=Addiction Research Center Inventory; PCAG=Penitobarbital-Chlorpromazine Alcohol Group subscale of the ARCI; LSD=Lysergic Acid Diethyl Amide subscale of the ARCI; MBG=Morphine Benzodrine Group subscale of the ARCI; AMPH=Amphetamine subscale of the ARCI; BG=Benzedrine Group subscale of the ARCI; VAS=Visual Analog Scale.

^aThese terms refer to the main effect of training condition in the repeated measures of analysis of variance using data that were obtained from the four training and four test-of-acquisition sessions in which participants met criterion for acquisition of the discrimination.

Table 2

Subject Ratings on the Pharmacological Drug Class Questionnaire During Testing

Dose (mg/kg)	Placebo	Opiate	Phenothiazine	Barbiturate	Antidepressant	Opiate Antagonist	Hallucinogen	Benzodiazepine	Stimulant	Phencyclidine
30*	1	0	0	0	1	1	0	0	0	0
60	2	0	0	0	0	2	0	0	0	0
120	3	0	0	0	1	0	0	0	0	0
30	0	0	0	0	0	4	0	0	0	0
60	0	0	0	0	0	4	0	0	0	0
120*	0	0	0	0	0	3	0	0	0	0
30*	1	1	0	1	0	1	0	0	0	0
60*	2	0	0	0	0	2	0	0	0	0
120	2	0	0	1	1	1	0	0	0	0
30	1	0	0	0	0	4	0	0	0	0
60	1	0	0	0	0	4	0	0	0	0
120	0	0	0	1	0	3	1	0	0	0

Note:

* Data for one subject is missing due to computer error