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Short communication

Safety of oral dronabinol during opioid withdrawal in humans

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ABSTRACT

Background: Opioid dependence remains a significant public health problem worldwide with only three FDA-approved treatments, all targeting the mu-opioid receptor. Dronabinol, a cannabinoid (CB) 1 receptor agonist, is currently under investigation as a novel opioid withdrawal treatment. This study reports on safety outcomes of dronabinol among adults in opioid withdrawal.
Methods: Twelve adults physically dependent on short-acting opioids participated in this 5-week within-subject, randomized, double blind, placebo-controlled inpatient study. Volunteers were maintained on oral oxycodone 30 mg qid. Double-blind placebo substitutions occurred for 21 h before each of 7 experimental sessions in order to produce opioid withdrawal. A single oral test dose was administered each session (placebo, oxycodone 30 and 60 mg, dronabinol 5, 10, 20, and 30 mg [decreased from 40 mg]). Heart rate, blood pressure, respiratory outcomes and pupil diameter were assessed repeatedly.
Results: Dronabinol 40 mg produced sustained sinus tachycardia accompanied by anxiety and panic necessitating dose reduction to 30 mg. Sinus tachycardia and anxiety also occurred in one volunteer after dronabinol 20 mg. Compared to placebo, dronabinol 20 and 30 mg produced significant increases in heart rate beginning 1 h after drug administration that lasted approximately 2 h ($p < 0.05$). Dronabinol 5 and 10 mg produced placebo-like effects. Oxycodone produced prototypic mu-opioid agonist effects (e.g., miosis).
Conclusion: Dronabinol 20 mg and higher increased heart rate among healthy adults at rest who were in a state of opioid withdrawal, raising concern about its safety. These results have important implications for future dosing strategies and may limit the utility of dronabinol as a treatment for opioid withdrawal.

1. Introduction

Opioid dependence is a significant public health problem worldwide that continues to grow, in large part, due to the prescription opioid epidemic. In 2013, within the United States (US), there were 1.9 million individuals with a prescription opioid use disorder and 712,000 with a heroin use disorder (Substance Abuse Mental Health Services Administration (SAMHSA), 2014). Currently, there are only three marketed FDA-approved medications (methadone, buprenorphine and naltrexone) for opioid dependence treatment, and all exert their efficacy through action at the mu-opioid receptor.

Dronabinol, a schedule III oral synthetic Δ^9-tetrahydrocannabinol (THC) analogue and cannabinoid-1 (CB1) receptor agonist, is currently approved for chemotherapy-induced nausea and vomiting and anorexia in patients with acquired immunodeficiency syndrome (AIDS). Interestingly, CB1 receptors are often co-localized with opioid receptors in brain regions involved in opioid withdrawal, drug reward and self-administration, and analgesia, including the locus coeruleus, nucleus accumbens, thalamus and spinal cord (Pickel et al., 2004; Scavone et al., 2010; Welch, 2009). Thus, CB1 agonists may have a role in modulating opioid-mediated effects, including the expression of opioid withdrawal (Scavone et al., 2013).

Preclinical studies have reported that CB1 agonists (i.e., Δ^9-THC) attenuate signs of opioid withdrawal (Lichtman et al., 2001; Cichewicz and Welch, 2003), while conversely; CB1 antagonists (SR 141716A) elicit opioid withdrawal signs (Navarro et al., 1998). One recent randomized placebo-controlled clinical study reported that dronabinol (30 mg/day) briefly and modestly reduced subject-rated

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opioid withdrawal severity; however, open-label buprenorphine on day 2 and other ancillary medications on multiple days also were given and no physiologic data (e.g., heart rate) were reported (Bisaga et al., 2015).

Safety outcomes from a study evaluating the efficacy of acute doses of oral dronabinol (without adjuvant medications) for the treatment of opioid withdrawal are reported here. Because there were statistically and clinically significant effects on heart rate and there is interest in exploring this class of agents for opioid dependence, the study team believed these results warranted quick dissemination (primary efficacy analyses to be reported separately).

2. Methods

2.1. Participants

Inclusion criteria were: age 18–50 years; self-report of non-medical use of short-acting opioids ≥21/30 days; opioid physical dependence; positive urine opioid test; and good general health as determined by physical exam, 12-lead ECG, and blood and urine chemistries. Exclusion criteria included: currently seeking treatment or pregnant/breastfeeding; physiologic dependence on alcohol or sedative/hypnotics requiring medical management; buprenorphine or methadone as primary drug of abuse; ongoing medical (e.g., chronic pain) or psychiatric (e.g., schizophrenia) illness; recent use of CYP3A4/2D6 medications; and use of marijuana >15/30 days in order to exclude daily or near daily users who could be tolerant to the effects of Δ^9-THC. The protocol was written and carried out in accordance with the Declaration of Helsinki, was approved by the University of Kentucky (UK) Institutional Review Board, and participants provided written informed consent.

2.2. Study setting

Participants resided as inpatients on the UK research unit for 5 weeks and were maintained on a caffeine-free diet. Urine was tested daily for the presence of illicit drugs and weekly for pregnancy (female). Cigarette smoking was allowed under staff supervision, except for 30 min before and throughout experimental sessions. Non-psychoactive medications (i.e., acetaminophen, colace) were available as needed, but restricted from midnight before session through session completion.

2.3. Study design, procedure and experimental sessions

This study employed a double-blind, randomized, within subject design. Participants were stabilized on oral oxycodone 30 mg qid (8:00, 12:00, 18:00, 22:00) for at least 5 days before completing a placebo training session followed by 7 experimental sessions at ≥72 h intervals. Sessions were from 09:00 to 16:00. Oral oxycodone maintenance continued throughout the study except on session days, when double-blind placebo was substituted for the three oxycodone maintenance doses preceding each session to produce spontaneous opioid withdrawal (mean baseline visual analogue scale score was 69.0 for "How severe is your OPIOID WITHDRAWAL?" scored from 0 "not at all" to 100 "extremely"). In addition, on session days, the 12:00 oxycodone maintenance dose was omitted because each session evaluated a single oral test dose at 10:00: dronabinol (5, 10, 20, or 40 mg), oxycodone (30 or 60 mg), or placebo. Only the first two subjects received dronabinol 40 mg due to safety concerns (see Section 3). This dose was then reduced to 30 mg. Thereafter, the dose order was fully randomized except that dronabinol 20 mg always preceded 30 mg. With regard to dronabinol dose selection, the principal investigator (SLW) initially proposed 30 mg as the highest test dose, but the sponsor required that the higher 40 mg dose be tested.

2.4. Drugs

Drugs were prepared by the UK Investigational Pharmacy under an Investigational New Drug Application (#69,214). Oxycodone HCl 30 mg tablets (Mallinckrodt Inc., Hazelwood, MD), lactose monohydrate powder N.F. (Medisca Pharmaceuticals, Plattsburgh, NY), and dronabinol 5 and 10 mg capsules (PAR Pharmaceutical, Spring Valley, NY) were used to prepare oxycodone, placebo, and dronabinol doses, respectively. All active doses were loose-filled with lactose before being over-encapsulated in order to maintain the blind.

2.5. Physiologic measures

During sessions, heart rate (HR), blood pressure, and oxygen saturation (Dinamap Non-Invasive Patient Monitor, GE Medical Systems, Tampa, FL) were measured every minute, beginning 30 min before drug administration. Respiration rate and end-tidal carbon dioxide ($EtCO_2$) levels (N-85 Capnograph, Nellcor, Boulder, CO) along with pupil diameter (Pupillometer, PLR-200, NeurOptics, Irvine, CA) were assessed every 15 min, beginning 30 min before drug administration.

2.6. Data analysis

Physiologic measures collected every minute were averaged across 15-min intervals and evaluated employing a two-factor repeated measures model (dose [placebo; oxycodone 15, 30 mg; dronabinol 5, 10, 20, 30 mg] × time). Peak maximum and minimum values were analyzed with a one-factor (dose) model. Significant results were evaluated with Dunnett post-hoc comparisons of placebo to active doses. Analyses utilized Proc Mixed in SAS 9.3 (SAS Institute, Inc., Cary, NC). Statistical significance was set at $p < 0.05$. Means (standard errors) are reported.

3. Results

3.1. Demographics

Twelve participants (6 females, all Caucasian) completed the study. They were 31.3 (±1.5) years old, completed 11.8 (±0.6) years of school, and used opioids (heroin and non-medical prescription opioids) 26.0 (±1.0) of the past 30 days. Nine were using heroin and prescription opioids, one was using heroin only, and two were using prescription opioids only. Six were injecting opioids. Eleven were tobacco smokers [Fagerstrom score: 4.4 (±0.7)]. Two used marijuana in the last 30 days (range: 1–2 days of use). Other substances used infrequently in the past 30 days included alcohol ($n = 4$), benzodiazepines ($n = 2$), and buprenorphine ($n = 4$).

3.2. Physiologic outcomes

The first two subjects receiving dronabinol 40 mg experienced sinus tachycardia (see Fig. 1), and both described having an "anxiety attack" that was assessed as similar to a panic attack by the study psychiatrist. The tachycardia lasted approximately 2 h. Systolic blood pressure (SBP) and heart rate increased for these two subjects, but diastolic blood pressure (DBP) response was more variable (see Fig. 1). Neither experienced dizziness nor chest pain. Both reported feeling normal by the end of session with vital signs returning to near baseline levels.

The remaining 10 subjects completed the amended protocol with 30 mg as the highest dronabinol dose. One did not receive the 30 mg dose because they were unable to tolerate the 20 mg