Drug and Alcohol Dependence 129 (2013) 116–124

Contents lists available at SciVerse ScienceDirect

Drug and Alcohol Dependence

journal homepage: www.elsevier.com/locate/drugalcdep

Abuse liability and reinforcing efficacy of oral tramadol in humans

Shanna Babalonis[a,b,*], Michelle R. Lofwall[a,b,c], Paul A. Nuzzo[b], Anthony J. Siegel[c], Sharon L. Walsh[a,b,c,d]

[a] University of Kentucky College of Medicine, Department of Behavioral Science, United States
[b] University of Kentucky, Center on Drug and Alcohol Research, United States
[c] University of Kentucky College of Medicine, Department of Psychiatry, United States
[d] University of Kentucky College of Medicine, Department of Pharmaceutical Sciences, United States

ARTICLE INFO

Article history:
Received 6 July 2012
Received in revised form
24 September 2012
Accepted 24 September 2012
Available online 23 October 2012

Keywords:
Tramadol
o-Desmethyltramadol (M1)
Human
Self-administration
Codeine
Oxycodone

ABSTRACT

Background: Tramadol, a monoaminergic reuptake inhibitor, is hepatically metabolized to an opioid agonist (M1). This atypical analgesic is generally considered to have limited abuse liability. Recent reports of its abuse have increased in the U.S., leading to more stringent regulation in some states, but not nationally. The purpose of this study was to examine the relative abuse liability and reinforcing efficacy of tramadol in comparison to a high (oxycodone) and low efficacy (codeine) opioid agonist.
Methods: Nine healthy, non-dependent prescription opioid abusers (6 male and 3 female) participated in this within-subject, randomized, double blind, placebo-controlled study. Participants completed 14 paired sessions (7 sample and 7 self-administration). During each sample session, an oral dose of tramadol (200 and 400 mg), oxycodone (20 and 40 mg), codeine (100 and 200 mg) or placebo was administered, and a full array of abuse liability measures was collected. During self-administration sessions, volunteers were given the opportunity to work (via progressive ratio) for the sample dose or money.
Results: All active doses were self-administered; placebo engendered no responding. The high doses of tramadol and oxycodone were readily self-administered (70%, 59% of available drug, respectively); lower doses and both codeine doses maintained intermediate levels of drug taking. All three drugs dose-dependently increased measures indicative of abuse liability, relative to placebo; however, the magnitude and time course of these and other pharmacodynamic effects varied qualitatively across drugs.
Conclusions: This study demonstrates that, like other mu opioids, higher doses of tramadol function as reinforcers in opioid abusers, providing new empirical data for regulatory evaluation.

1. Introduction

Tramadol, marketed in the United States (U.S.) since 1995 to treat mild-to-moderate pain, is structurally similar to morphine and codeine but produces its analgesic effects through two mechanisms. It has minimal affinity for the μ-opioid receptor and inhibits the reuptake of serotonin and norepinephrine (Raffa et al., 1992; Desmeules et al., 1996). The active hepatic metabolite, *o*-desmethyltramadol or M1, is an opioid agonist with high relative intrinsic efficacy and moderate affinity for the μ-opioid receptor (Gillen et al., 2000; Raffa et al., 1992; Volpe et al., 2011).

Historically, tramadol has been considered to have limited abuse liability and was introduced in the U.S. as an unscheduled analgesic. Prior to its U.S. approval, tramadol was marketed in Europe for approximately 20 years with little evidence of abuse or diversion (Radbruch et al., 1996). Epidemiological studies conducted after its U.S. marketing indicated that tramadol misuse was rather low compared to hydrocodone or oxycodone (Cicero et al., 1999, 2005; Inciardi et al., 2006). Preclinical abuse liability assessments have generally supported its limited abuse potential, as tramadol produced modest rates of IV self-administration relative to prototypic opioids like morphine (O'Connor and Mead, 2010; Yanagita, 1978).

Early clinical studies also yielded no abuse liability signal for tramadol from experienced opioid users. Examination of intramuscular (IM: 75, 150, and 300 mg) and intravenous (IV: 100 and 200 mg) tramadol indicated that the lower IM doses (75 and 150 mg) were placebo-like, while higher IM doses and IV doses produced self-reported global drug effects but did not produce miosis or increase abuse liability measures (Preston et al., 1991; Epstein et al., 2006). The acute effects of tramadol (100 and 300 mg; IM) were examined in methadone-maintained volunteers, and these doses did not produce agonist-like effects or precipitate withdrawal (Cami et al., 1994).

Epidemiological reports and surveillance studies have indicated that tramadol diversion, abuse and overdose have recently increased in the U.S. (Dart et al., 2011; Spiller et al., 2010; Watson

* Corresponding author at: University of Kentucky College of Medicine, Department of Behavioral Science, Lexington, KY 40536-0086, United States.
Tel.: +1 859 257 1881.
E-mail address: babalonis@uky.edu (S. Babalonis).

0376-8716/$ – see front matter © 2012 Elsevier Ireland Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.drugalcdep.2012.09.018

et al., 2003; SAMHSA, 2007), leading several states (Kentucky, Arkansas, Wyoming and Tennessee) to change it to a more stringent category (Schedule IV), while it remains unscheduled nationally. Recent clinical research suggests that the abuse liability of tramadol may have been previously underestimated with respect to oral administration, as the earlier preclinical and clinical studies employed parenteral dosing. As production of the opioid-agonist metabolite, M1, is largely dependent on hepatic metabolism, concentrations of M1 are much higher after oral, relative to parenteral administration (Ardakani and Rouini, 2007; Enggaard et al., 2006; Poulsen et al., 1996; Campanero et al., 1999), likely resulting in greater opioid agonist effects after oral administration. Jasinski et al. (1993) evaluated oral tramadol (175, 350, and 700 mg) in non-dependent, opioid-experienced users and reported higher doses of oral tramadol (350 and 700 mg) produced miosis, increased ratings on abuse liability measures (e.g., drug liking, MBG scale of ARCI), and were identified as opioid-like on a pharmacological class questionnaire (Jasinski et al., 1993; Epstein et al., 2006). These effects were similar in magnitude to those produced by oral oxycodone (20 and 40 mg) but with a delayed onset (Jasinski et al., 1993; Epstein et al., 2006). Higher (200 and 400 mg), but not lower doses (50 and 100 mg) of oral tramadol produced hydromorphone-like drug discrimination responding in opioid abusers; no doses produced effects on VAS measures associated with abuse liability (e.g., like drug effects, good drug effects; Duke et al., 2011). Opioid agonist effects have also been observed in naïve/light opioid users, whereby a therapeutic dose of oral tramadol (100 mg) increased scores on several subjective measures (e.g., like drug, want to take drug again) similar to oral morphine (Zacny, 2005). Further evidence of the opioid agonist action arises from reports that oral tramadol may suppress spontaneous opioid withdrawal (Lofwall et al., 2007; trend reported in Carroll et al., 2006). Naloxone challenge or cessation of chronic oral tramadol also leads to dose-dependent opioid-like withdrawal signs/symptoms (Lanier et al., 2010; Barsotti et al., 2003; Freye and Levy, 2000), although additional atypical withdrawal symptoms, such as anxiety, confusion and hallucinations, have been reported (Senay et al., 2003).

Given the dramatic increase in prescription opioid abuse in the U.S., along with emerging signals of tramadol abuse and overdose, further evaluation of the abuse liability of therapeutic and supratherapeutic doses of tramadol is warranted. The purpose of this study was to examine directly the relative abuse liability and reinforcing efficacy (measured via self-administration) of oral tramadol compared to oxycodone, a high efficacy μ-opioid agonist with known abuse liability, codeine, a moderate affinity μ-opioid agonist with relatively low abuse liability, and placebo in a cohort of non-dependent prescription opioid abusers.

2. Methods

2.1. Participants

Participants were healthy, adult prescription opioid abusers who were not physically dependent on opioids. All volunteers were recruited by local advertisements and paid for participation. Participants completed an on-site evaluation, including an investigator interview, medical history and physical examination, ECG, blood chemistry and urinalysis. Volunteers were literate, English-speaking adults, ages 18–50. Individuals seeking treatment for substance abuse, successfully maintaining abstinence, or with significant medical problems (e.g., seizure disorders, asthma), serious psychiatric illness (e.g., schizophrenia), current physiological drug dependence or pregnancy were excluded. All participants reported illicit use of prescription opioids confirmed by urine drug testing. Participants were also required to provide an opioid negative urine sample in the absence of opioid withdrawal symptoms to exclude physiological opioid dependence. All participants provided sober, written informed consent prior to participation. This study was approved by the University of Kentucky (UK) Medical Institutional Review Board and a Certificate of Confidentiality was obtained from the National Institute on Drug Abuse. All study procedures were conducted in accordance with the Helsinki guidelines for ethical research.

2.2. Drugs

This study was conducted under an investigator-initiated Investigational New Drug Application from the Food and Drug Administration (#69,214). All study medications were stored and prepared by the UK Investigational Pharmacy. Oxycodone hydrochloride (Spectrum Chemical Manufacturing Corp., Gardena, CA), tramadol hydrochloride and codeine phosphate powders (both from Medisca, Plattsburgh, NY) were weighed and packed into uniformly appearing size 0 capsules (Health Care Logistics, Circleville, OH). Lactose (Mallinckrodt Chemical, Paris, KY) was used for the placebo condition and for filler in the active dose capsules.

2.3. Study design

This 4-week inpatient study utilized a within-subject, randomized, double-blind, placebo controlled design and examined oral tramadol (200 and 400 mg), oxycodone (20 and 40 mg), codeine (100 and 200 mg) and placebo. Volunteers resided at the Clinical Research Development and Operations Center, a closed inpatient hospital research unit, and participated in a total of 7 pairs of experimental sessions (14 sessions total): 7 sample and 7 self-administration sessions.

2.4. General methods

Participants were trained on study procedures using a Macintosh Mini computer (Cupertino, CA) and were accompanied by a trained research assistant during each session. Participants received a caffeine-free diet and were provided a standardized, light breakfast 2 h before experimental sessions. Smoking was permitted up to 30 min prior to the start of sessions. Ad libitum smoking was permitted after sessions and on non-session days. Urine samples were collected each morning and tested for drugs of abuse; females were tested for pregnancy daily. Breath samples were obtained before each session and tested for alcohol.

2.4.1. Sample sessions. Sample sessions were 6.5 h in length. At the beginning of sample sessions, participants were reminded to pay close attention to the drug effects, as they would be given the opportunity to earn some, none or all of the same drug dose the next day. An array of measures was collected prior to and at regular intervals after drug administration (see below).

2.4.2. Self-administration sessions. Self-administration sessions were 1.5–4.5 h in length and were conducted 24 h after each sample session. Selected safety measures were collected at baseline and at 0.5 h intervals after drug administration. Participants were given a total of 7 opportunities (i.e., trials) to respond on a progressive ratio (PR) schedule to earn portions of the sample dose (in 1/7th increments) or a portion of money (a total of $21 available, in increments of $3). Participants responded on the PR schedule via clicks on a computer mouse. The response requirement successively increased across the 7 trials: 50, 250, 500, 1000, 1500, 2000 and 2500 responses, with a total of 7800 responses necessary to earn all of the available drug or money over a maximum of 210 min. As each reinforcer operated under an independent PR schedule, responding for one reinforcer did not impact response requirements for the other reinforcer. When PR responding was completed, the participants received the amount of drug or money earned. Cash was delivered to the volunteer, but kept in a locked location until study completion. If drug was administered, participants were monitored and safety data collected for 3 h.

2.4.3. Physiological measures. Heart rate, blood pressure and oxygen saturation (Dinamap Non-Invasive Patient Monitor, GE Medical Systems, Tampa, FL) were collected every minute 30 min before and for 6 h after sample drug administration. Respiration rate, expired end tidal CO_2 (N-85 Capnograph, Nellcor, Boulder, CO) and pupil diameter measurements (PLR-200, NeurOptics, Irvine, CA) were measured at baseline, every 15 min after sample drug administration for the first 2.5 h, and every 30 min for the remaining 3.5 h.

2.4.4. Subjective and observer-rated measures. Subjective effects measurements during sample sessions included a six-item Visual Analog Scale (VAS; Middleton et al., 2012), collected at baseline and in 15-min intervals for the first 2.5 h, then every 30 min for the remaining 3.5 h; the Addiction Research Center Inventory (ARCI) short form (Martin et al., 1971), presented at baseline and 2 h and 4 h after drug administration; the Pharmacological Class Questionnaire (Jasinski et al., 1977), collected once, 6 h post-dose; a drug street value measure, presented in 30-min intervals after drug administration; and Participant-Rated Opioid Adjective Scale (Fraser et al., 1961), presented at baseline and at 30-min intervals post-dose. Trained research assistants rated signs of opioid agonist effects on the Observer-Rated Opioid Adjective Scale (Fraser et al., 1961) at baseline at 30-min intervals after drug administration. For further detail on these measures, please see Walsh et al. (2008) for full descriptions.

2.4.5. Performance and ocular measures. The Flicker-Fusion Task, an ocular measure that is sensitive to the visual perception-impairing effects of opioids (Walsh et al., 2008; Stoops et al., 2010) and a 90-s computerized version of the DSST (adopted