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The relative abuse liability of oral oxycodone, hydrocodone and hydromorphone assessed in prescription opioid abusers

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Abstract

Abuse of prescription opioids has risen precipitously in the United States. Few controlled comparisons of the abuse liability of the most commonly abused opioids have been conducted. This outpatient study employed a double-blind, randomized, within-subject, placebo-controlled design to examine the relative abuse potential and potency of oral oxycodone (10, 20 and 40 mg), hydrocodone (15, 30 and 45 mg), hydromorphone (10, 17.5 and 25 mg) and placebo. Healthy adult volunteers ($n = 9$) with sporadic prescription opioid abuse participated in 11 experimental sessions (6.5 h in duration) conducted in a hospital setting. All three opioids produced a typical *mu* opioid agonist profile of subjective (increased ratings of liking, good effects, high and opiate symptoms), observer-rated, and physiological effects (miosis, modest respiratory depression, exophoria and decrements in visual threshold discrimination) that were generally dose-related. Valid relative potency assays revealed that oxycodone was roughly equipotent to or slightly more potent than hydrocodone. Hydromorphone was only modestly more potent (less than two-fold) than either hydrocodone or oxycodone, which is inconsistent with prior estimates arising from analgesic studies. These data suggest that the abuse liability profile and relative potency of these three commonly used opioids do not differ substantially from one another and suggest that analgesic potencies may not accurately reflect relative differences in abuse liability of prescription opioids.

Keywords: Hydrocodone; Oxycodone; Hydromorphone; Human; Opioid; Abuse liability; Analgesia; Prescription opioids

1. Introduction

Rates of prescription opioid abuse have been on the rise in the United States for the past several years (Compton and Volkow, 2006; Zacny et al., 2003) and may be increasing elsewhere in the world, including, for example, in Australia (Mouzos et al., 2007). Data from the 2006 National Survey on Drug Use and Health (NSDUH) indicate that 4.7 million Americans used a prescription opioid illicitly in the month preceding the survey (SAMHSA, 2007b), and approximately one million people in 2006 were estimated to be prescription opioid-dependent (based upon DSM-IV criteria), adding to the nearly one million people estimated by the Office of National Drug Control Policy to be chronic users of heroin (ONDCP, 2001). The number of new illicit users of prescription opioids has grown to over 2 million, up from 1.5 million in 1999, representing over a 5-fold increase from the mid-1980s when there were approximately 400,000 new initiates per year. One review suggests that the relative prevalence of opioid prescription abuse may be comparable to the prevalence of heroin and cocaine abuse (Zacny et al., 2003). For those individuals initiating illicit drug use for the first time, the most recent epidemiological data indicate that prescription opioids have now surpassed marijuana as the most common drug(s) of initiation (SAMHSA, 2007b). The 2006 Monitoring the Future survey, a national survey of drug use among 8th, 10th and 12th graders, reported stable or declining rates of use for most illicit drugs; however, rates of Oxycontin® and Vicodin® use increased in nearly all grade levels, with the highest rate estimates indicating that nearly 10% of all 12th graders have used Vicodin® (Johnston et al., 2007). Moreover, survey data indicate that about half of teens (grades 7–12) do not believe that there is a great risk in abusing prescription medicine and

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30% believe that prescription pain relievers are non-addictive (PATS, 2005).

Hydrocodone (also known as dihydrocodeinone) is a semi-synthetic full *mu* opioid agonist related to codeine that is metabolized by cytochrome P450 2D6 and transformed into another *mu* agonist, hydromorphone (Otton et al., 1993); however, this conversion does not appear to be critical to the abuse potential of hydrocodone (Kaplan et al., 1997). Hydrocodone is marketed in the United States for use as an antitussive and analgesic and, while hydrocodone itself is listed under Schedule II, it is only sold in combination formulations (e.g., with acetaminophen – Lortab® and Vicodin®), which are regulated under the less restrictive Schedule III category. Hydrocodone is the most frequently prescribed opioid in the United States with an estimated 130 million prescriptions in 2006, up from approximately 88 million in 2000 (IMS National Prescription Audit Plus™). Given its broad availability, it is no surprise that hydrocodone accounts for the greatest proportion of emergency room drug use mentions for the prescribed opioids (and has shown successive increases since 1996) according to the Drug Abuse Early Warning Network (DAWN), a national data collection system that systematically monitors drug abuse through hospital emergency departments in the contiguous United States (SAMHSA, 2007a).

Oxycodone (dihydrodydroxycodienone) is a semi-synthetic opioid that has been in clinical use for more than 90 years. Oxycodone is manufactured and marketed in the United States in numerous oral formulations, although oxycodone is widely used in other countries by the intravenous, intramuscular and rectal routes. Oxycodone is a full *mu* opioid agonist, metabolized by the P450 2D6 enzyme to at least one active metabolite, oxymorphone (Beaver et al., 1978), which is itself marketed as an analgesic. Historically, oxycodone was considered to be associated with a lower abuse liability, similar to that of codeine, because it was initially introduced to the United States in 1981 in combination with over-the-counter non-opioid analgesics (Poyhia et al., 1993). Oxycontin®, a sustained release formulation of oxycodone, has been identified in the lay press as an especially problematic and dangerous drug of abuse because it is available in higher dosages than other oxycodone formulations, and the sustained release feature can be readily bypassed by crushing the tablets. However, Oxycontin®, immediate release oxycodone (e.g., Roxicodone®) and oxycodone combination products with either acetaminophen (e.g., Percocet®) or aspirin (e.g., Percodan®), all regulated under Schedule II, have historically accounted for a smaller portion of prescription opioid sales (estimated to be about 15% of the market in 2001 based upon the IMS National Prescription Audit Plus™) than those for hydrocodone, propoxyphene or codeine products. However, recent data from the Drug Enforcement Agency (http://www.deadiversion.usdoj.gov/quotas/quota_history.htm) indicate that, while licit aggregate production for hydrocodone has increased approximately 2.8-fold between 1998 and 2008 (from 16,314,000 to 45,200,000 kg), production of oxycodone has increased nearly 6-fold (from 12,118,000 kg to nearly 75,000,000 kg) over the same 10-year period, reflecting the increasing availability of, demand for, and exposure to both prescription opioids. Moreover, data from recent DAWN reports suggest that oxycodone mentions are increasing in number, approaching the number of hydrocodone mentions (SAMHSA, 2007a).

Hydromorphone, a semi-synthetic opioid derived from morphine, is a full mu agonist that has been used clinically for more than 75 years and is typically reserved for the treatment of severe pain. It is presently marketed in formulations for oral, rectal and parenteral use. While production of hydromorphone has also increased over the past decade, its clinical use is less widespread as evidenced, in part, by substantially lower aggregate production (e.g., only 3.3 million kg in 2008) compared to oxycodone and hydrocodone. In early 2005, a novel sustained release formulation (Palladone®) of hydromorphone was introduced onto the U.S. market; however, sale of the product was suspended within months subsequent to pronounced synergistic effects when taken in combination with alcohol, which were reported to represent a substantively greater risk than the typical interaction of other mu opioid agonists when taken in combination with alcohol. The purpose of this study was to examine the relative abuse liability of hydrocodone and oxycodone in comparison to hydromorphone by examining a range of doses, including supratherapeutic doses, in individuals who reported sporadic recreational use of prescription opioids. Despite the widespread clinical use of oxycodone and hydrocodone, comparatively few studies have directly evaluated the abuse liability and clinical pharmacology of these commonly abused opioids. Most available data assessing the relative potency of these compounds to produce their direct effects has emanated from the pain literature where the drugs are compared on their relative efficacy as analgesics rather than measures related to abuse liability.

2. Methods

2.1. Participants

Participants were adult volunteers who used prescription opioids illicitly for their psychoactive effects but were not physically dependent on opioids at the time of the study (for details see Section 3.1). Volunteers were recruited through local advertisements and were paid for their participation. Individuals who were seeking treatment for their substance abuse or successfully sustaining abstinence in the community were excluded. Study enrollment was continuous, and a maximum of four volunteers could participate simultaneously.

All participants were determined to be in good health by medical history and physical examination, an electrocardiogram and laboratory tests. Subjects were carefully screened to eliminate those presenting with seizure disorders, history of asthma or other respiratory disorders, head injury, hypertension, cardiovascular disease or abnormal ECG. All participants reported illicit use of opioids, and this use was confirmed by objective urinalysis results during the screening period. This study was approved by the University of Kentucky Institutional Review Board, and subjects gave their written informed consent prior to participation. A Certificate of Confidentiality was obtained from the National Institute on Drug Abuse for the project. This study was conducted in accordance with the Helsinki guidelines for ethical human research.

Subjects participated as outpatients in this study and were instructed that they needed to abstain from illicit drug use during their participation. Each study day urine specimens and breathalyzer tests were obtained and tested for illicit drugs, including methadone, cocaine, THC, benzodiazepines, morphine-derived opioids, amphetamine, barbiturates, methamphetamine, phencyclidine, tricyclic antidepressants (Multi-Drug Screen Test Dip Card 10 panel; American Screen Corp., Louisiana), oxycodone (Single Oxy Dip Card; American Screen