Journal of Pharmacological and Toxicological Methods 75 (2015) 118–129

Contents lists available at ScienceDirect

Journal of Pharmacological and Toxicological Methods

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

Original article

Abuse liability assessment of hydrocodone under current draft regulatory guidelines

David V. Gauvin *, Margaret McComb, Robert Code, Jill A. Dalton, Theodore J. Baird

Department of Safety Pharmacology and Neurobehavioral Sciences, MPI Research Inc., Mattawan, MI, United States

ARTICLE INFO

Article history:
Received 11 February 2015
Received in revised form 10 April 2015
Accepted 4 May 2015
Available online 9 May 2015

Keywords:
Hydrocodone
Self administration
Drug discrimination
Drug dependence
Discontinuation syndrome
Withdrawal
Morphine
Oxycodone
Abuse liability
Methods

ABSTRACT

Introduction: The abuse liability of hydrocodone was assessed in male Sprague–Dawley rats under the European Medicines Agency, the International Commission on Harmonisation, and the U.S. Food & Drug Administration draft guidelines for the non-clinical investigation of the dependence potential of medicinal products.
Methods: Self-administration, drug discrimination, and repeat-dose two week dependence liability studies were conducted to compare hydrocodone to the prototypical opiates, morphine and oxycodone.
Results: Hydrocodone was self-administered, produced an opiate-like subjective discriminative generalization profile and produced a significant discontinuation syndrome following abrupt treatment cessation that was quantitatively and qualitatively similar to morphine and/or oxycodone.
Conclusion: Hydrocodone has abuse liability more similar to Schedule II opiates than other Schedule III compounds currently controlled under the U.S. Controlled Substance Act.

1. Introduction

Guidelines for regulatory review of all new psychoactive substances for both human and veterinary approval have been disseminated by the European Monitoring Centre for Drug and Drug Addiction (EMCDDA, 2009), the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMEA, 2006), the International Conference on Harmonisation (ICH, M3[R2], 2009), and the United States Food and Drug Administration (FDA, 2010). These guidelines are intended to 1) help define the scope of the term "psychoactive substances" and, 2) to put in place a sound methodological and procedural basis for carrying out risk assessments in regard to health and social risks of the use of, manufacture of, and traffic in these new psychoactive substances that involve member states of both the 1961 United Nations Single Convention on Narcotic Drugs and the 1971 United Nations Convention on Psychotropic Substances.

A three-part, evidence-based preclinical risk assessment plan requires standardized behavioral assays of self-administration, drug discrimination, and dependence potential to be conducted in either rodents (contemporarily considered the primary model) or non-human primates. The results of these assays must be supplied prior to health agency approval of any new chemical entity that 1) crosses the blood brain barrier; 2) is pharmacologically similar to any known drug of abuse; 3) has a novel mechanism of action; 4) produces psychoactive effects such as sedation, euphoria, or mood changes; or 5) has any direct or indirect actions on other neurotransmitter systems associated with abuse potential, such as dopamine, norepinephrine, GABA, acetylcholine, opioid, NMDA, and cannabinoid.

The chemical 4,5α-epoxy-3-methoxy-17-methyl-morphinan-6-one was given the drug name, dihydrocodeinone, when it was first marketed in Germany in the early 1920's it sold under the proprietary name of Dicodid®. It was never screened for abuse liability prior to approval as a medicinal product. As translated and cited by Eddy, Halbach, and Braenden (1957), hydrocodone addiction was reported as early as 1927:

> *Müller de la Fuenta said that cases of addiction to dicodid were known in 1927; 17 of the 280 questionnaires analysed by Wolff, in 1928, reported dicodid addiction; and in 1930 Richtzenhain warned that "dicodidismus" was then so often observed that one should be as cautious with dicodid injection as one would be with morphine.*

In the United States the nonproprietary or generic name adopted for the drug was simply, hydrocodone. Hydrocodone combination products

* Corresponding author at: Dept NBS, MPI Research Inc., 54943 North Main Street, Mattawan, MI 49071, United States. Tel.: +1 269 668 3336x1613; fax: +1 269 668 4151.
E-mail address: david.gauvin@mpiresearch.com (D.V. Gauvin).

http://dx.doi.org/10.1016/j.vascn.2015.05.003
1056-8719/

(i.e., Vicodin™, Hycotuss™), the only legitimate U.S. drug products on the market at the time, were placed into Schedule III of the Controlled Substances Act (21 USCA, Chapter 13 §801-971) in spite of differential control of its analgesic equivalents oxycodone (Roxicodone™, Percocet™) and morphine (Kadian™, MS-Contin™) into Schedule II.

The differential scheduling action was approved under the premise that the likelihood of acetaminophen toxicity would limit or minimize the abuse of hydrocodone pharmaceutical products (cf Commission on Narcotic Drugs: The Single Convention on Narcotic Drugs; Schedules: E/CN.7/AC.3/9/Add.1; 18 November 1958; Eddy, Halbach, & Braenden, 1956). In the conclusions of these early reviews, hydrocodone was considered to be pharmacologically equivalent to morphine with respect to analgesia, CNS depression, and dependence potential. Reports in the published literature and by the U.S. National Institute on Drug Abuse indicate that hydrocodone-combination products are consumed in large quantities without concomitant and significant changes in liver function profiles that might have been predicted based on, for example, acetaminophen content. The therapeutic effects of hydrocodone, its abuse potential, and actual abuse history in the US were thoroughly reviewed during the requisite 8-factor analyses for schedule control actions. Full literature reviews have been conducted by both U.S. DEA (2014) and U.S. Department of Health and Human Services (2014). More recently, hydrocodone single entity and combination products have been administratively placed into Schedule II (Drug Enforcement Administration, 2014).

The present studies were designed to systematically assess and compare the relative abuse liability of hydrocodone and the prototypical CII opiates, morphine and oxycodone, using an integrative approach consistent with the current standardized international regulatory guidelines.

2. Material and methods

2.1. Subjects

Male Sprague–Dawley rats ordered from Charles River Laboratories (Portage, MI), 7–8 weeks of age and weighing approximately 230–260 g were used in these experiments. The preponderance of the published reports of drug abuse models in animal species has indicated a selective use of male animals. It is generally assumed that the chronic nature of dosing regimens used in these studies render equi-effective responses in animal subjects; no gender-differences were expected in the direction, duration, or magnitude of behavioral and physiological effects induced by the procedures set forth in the study plans, and accordingly only males were used.

Animals in the self-administration and drug discrimination studies were singly housed in solid bottom poly-boxes with non-aromatic bedding. Animals in the drug dependence study were singly housed in standard stainless-steel wire-bottom cages. Solid-bottom cages bedding materials were not used in this latter study because 1) of the potential to induce pica (Batra & Schrott, 2011) and the incidence of copraphagia (Barnes & Fiala, 1958a,b, 1959; Barnes, Fiala, McGehee, & Brown, 1957; Iwomoto & Klaassen, 1977; Lugo & Kern, 2002; March & Elliott, 1954; Mullis, Perry, Finn, Stafford, & Sadée, 1979) in rats. Access to fecal boli containing behaviorally active concentrations of opiate and opiate-related metabolites, therefore, represents a significant experimental confound in such a study plan, and was avoided by the use of alternate wire bottom caging.

Fluorescent lighting was provided via an automatic timer for approximately 12:12 hour light:dark cycle per day. Temperature and humidity were monitored and recorded daily and maintained according to standard operating procedures between 64 to 79 °F and 30 to 70%, respectively. The basal diet was block Lab Diet® Certified Rodent Diet #5002 (PMI Nutrition International, Inc.). The diet and tap water were available ad libitum unless designated otherwise (see below). The protocols governing these studies had prior approval of MPI Research Institutional Animal Care and Use Committee.

2.2. Equipment

The self-administration and drug discrimination studies were conducted in standard rat two-lever operant chambers (ENV-008CT; Med Associates, Inc. NH, USA) with a modified top for self-administration (MED-008CT-B2) equipped with a syringe pump (PHM-100) located in a specially constructed and locked box located on top of the sound-attenuating cubicle (ENV-018MD). Each chamber was equipped with two stimulus lamps (ENV-221M), two retractable levers (ENV-112CM), house lamp (28 V DC, 100 mA, ENV 215M), a modular pellet dispenser (ENV 203N-45), and exhaust fan. The operant chamber was interfaced (SmartCtrl 8 Input, 16 Output Package) with an IBM-based personal computer system capable of controlling 16 chambers. An operant control and data collection software program for both drug discrimination and self-administration procedures (R. Code, MPI Research, Inc.) was written and validated using MED-PC language. A total of thirty-two identically-equipped chambers were used in these studies that were located in two security-controlled, video monitored, key-card accessed rooms of the test facility.

2.3. Surgery

Sterile surgical implantation of jugular catheters to enable the self-administration study was conducted by Charles River Laboratories (Portage, MI) using specially designed and manufactured catheters (MPI Research, Inc.). Eighty-six percent of all implanted catheters remained patent for up to 6 months under current laboratory standards and procedures (Gauvin, Dalton, Baird, & Faqi, 2013). Catheters were flushed regularly with normal sterile saline for injection (USP) and locked with heparinized solutions (30–100 IU/mL) of either 50% dextrose or saline throughout the life of the catheter to prolong patency. Saline flushing occurred immediately prior to and after self-administration sessions. Patency was verified daily with presession and postsession flushing of catheters. The resistance to flow was used as the first indicator of possible catheter occlusion. If catheter occlusion was suspected, a systems check on the viability of the implanted catheters was conducted. Technicians would administer a 5 mg/kg dose of methohexital (Brevital™), or any equivalent short-onset, short-lived barbiturate through the catheter. Animals were monitored for at least 5 min post injection for signs of lethargy, malaise, or unconsciousness. If the catheter was patent, the animal would appear anesthetized shortly following the infusion. Recovery from the system check would take approximately 15 min.

2.4. Procedures

2.4.1. Self-administration

Details of the self-administration training and testing procedure are similar to those previously described by Briscoe et al. (1999). The rat self-administration procedure that has been adopted by the industry and FDA is described as a single lever operant lever press response under a fixed-ratio 10 (FR10) schedule of cocaine deliveries with session lengths of at least 1 h duration. Once animals demonstrated day-to-day stability in responding for cocaine deliveries (less than 20% day-to-day variability in the total number of training drug deliveries for three consecutive days). Once each animal demonstrated stable operant responding for cocaine infusion (0.56 mg/kg/injection) for three contiguous days of training or maintenance sessions a series of test sessions were planned (A-B-A study design). The first series of test sessions was conducted with the maintenance dose of cocaine (0.56 mg/kg/injection) — in this session the animal, for the first time, was allowed to respond for an unlimited number of injections over a one-hour access period on each of three consecutive days. Following