Pharmacology, Biochemistry and Behavior 90 (2008) 787–796

Contents lists available at ScienceDirect

Pharmacology, Biochemistry and Behavior

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

Sex and opioid maintenance dose influence response to naloxone in opioid-dependent humans: A retrospective analysis

Mohit P. Chopra, Zachary Feldman, Michael J. Mancino, Alison Oliveto *

Department of Psychiatry and Behavioral Sciences, University of Arkansas for Medical Sciences, Little Rock, AR 72205, USA

ARTICLE INFO

Article history:
Received 30 October 2007
Received in revised form 22 May 2008
Accepted 31 May 2008
Available online 7 June 2008

Keywords:
Opiate dependence
Sex differences
Methadone maintenance
Naloxone-precipitated withdrawal
Humans
Naloxone
Placebo-controlled
Dose effect

ABSTRACT

Pooled self-report and physiological data from 32 male and 15 female methadone or *levo*-α-acetyl methadol (LAAM) maintained volunteers were retrospectively analyzed for individual differences in response to naloxone (0.15 mg/70 kg, IM) and placebo at 20 and 40 min post-injection. Males and females were each divided by the median split methadone maintenance dose (MMD, in mg/kg body weight) into high and low MMD groups and MMD was used as a factor in the analyses, along with sex, drug, and time post-drug. Females in the low, but not high, MMD group showed naloxone-induced increases in ratings on the Antagonist and Mixed-Action sub-scales of the Adjective Rating Scale, and the Lysergic acid diethyl amine (LSD) sub-scale of the Addiction Research Center Inventory at 20 min post-injection. Males in the high MMD group showed significant naloxone-induced increases in scores of these measures at both post-injection time-points. In addition, low MMD subjects showed more short-lived naloxone-induced increases on Visual Analogue Scale (VAS) Bad and Any drug effects ratings than high MMD subjects. These results suggest that those on a lower MMD, especially women, experience a more intense, but short-lived, response to naloxone, whereas those on a higher MMD experience a more modest, but longer-lasting effect.

1. Introduction

Even though more than 150,000 persons in the United States are in opiate maintenance treatment, about 40% of whom are female, (Levine et al., 2004; also available at: http://www.oas.samhsa.gov/ADSS/methadone.pdf), few controlled studies have examined how sex or maintenance opiate dose might explain individual differences during opiate withdrawal. Most published studies about opiate maintenance, including a 33-year follow-up of heroin addicts, have examined only males as participants in their cohort (Hser et al., 2001). There is evidence that males and females respond differently to a variety of commonly-used substances including alcohol (Fillmore et al., 1997; Lancaster and Spiegel, 1992), benzodiazepines (Jackson et al., 2005), cocaine (Singha et al., 2000), nicotine (Perkins et al., 2002) and opiates (Zacny, 2001; Zacny and Beckman, 2004). While sex differences in opioid antinociception or opioid-induced analgesia have been studied extensively for a number of different opiates (Barrett, 2006), a paucity of data exists regarding sex-related differences in opiate withdrawal in opioid-dependent humans. Hence, we performed a retrospective analysis of pooled data from five naloxone discrimination studies with the aim of examining potential sex and opiate-dose related differences in response to naloxone in opioid-maintained individuals (Oliveto et al., 1998, 2002, 2003a,b, 2004).

Evidence from animal studies indicates that male and female rodents differ in their response to opiates under several abuse-liability paradigms, including self-administration and other indirect measures of the reinforcing effects of opiates, such as conditioned place preference and locomotor activity (see reviews by Lynch et al., 2002; Carroll et al., 2004). For instance, female rats have been shown to acquire heroin self-administration at a faster rate than male rats (Lynch and Carroll, 1999; Carroll et al., 2002) and female rodents consumed greater amounts of opiates compared to the male rodents (Carroll et al., 2001; Alexander et al., 1978; Hadaway et al., 1979). In addition to consuming greater amounts of fentanyl compared to male rats, female rats were also seen to self-administer greater amounts of fentanyl during experimentally produced periods of chronic stress (Klein et al., 1997). Under a conditioned place preference paradigm, female rats demonstrated a much stronger preference for the place where they were administered morphine than where placebo was administered, compared to male rats (Randall et al., 1998). In addition, female rats were also shown to be less sensitive to the morphine-induced suppression of locomotor activity (Craft et al., 2006).

Similarly, sex-related differences have been demonstrated in the expression of physical dependence and withdrawal in rodents. For instance, naloxone produced greater withdrawal scores in male rats treated with morphine at 10 mg/kg body weight than in female rats receiving the same dose (Craft et al., 1999). Along similar lines, male mice demonstrated a significantly greater sensitivity to naloxone-

* Corresponding author. Department of Psychiatry, UAMS, 4301 West Markham Street, slot #843, Little Rock, AR 72205, USA. Tel.: +1 501 686 8969; fax: +1 501 526 7816.
E-mail address: olivetoalison@uams.edu (A. Oliveto).

0091-3057/$ – see front matter © 2008 Elsevier Inc. All rights reserved.
doi:10.1016/j.pbb.2008.05.023

precipitated withdrawal, as evidenced by their having an almost fourfold lower median effective dose (ED_{50}) for withdrawal compared to female mice (Kest et al., 2001). In contrast, Cicero et al. (2002) reported that no sex differences were observed during naloxone-precipitated withdrawal following chronic morphine administration, although male rats exhibited a more severe spontaneous withdrawal syndrome than female rats following abrupt cessation of morphine administration. Although naloxone dose and morphine administration schedule differed across the three studies, Cicero et al. (2002) interpreted the absence of sex differences during naloxone-precipitated withdrawal between male and female rats at equivalent doses to mean that morphine produced equivalent levels of physical dependence in both male and female animals. The authors, however, also acknowledged their inability to offer a reasonable explanation of this observation. More recent studies in rodents suggest that both sex and opioid maintenance dose influence the nature of opioid dependence and withdrawal. In a study examining spontaneous opiate withdrawal in mice using low-dose and high-dose morphine administration paradigms, female mice demonstrated somatic withdrawal signs up to 24 h longer than that demonstrated by male animals. The same study showed that opiate withdrawal also varied as a function of the cumulative morphine dose administered, such that animals treated with high-dose morphine experienced more severe and longer-lasting withdrawal signs than those receiving a low cumulative dose (Papaleo and Contarino, 2006).

Accumulating evidence also suggests that there are sex differences in behavioral and subjective responses to opioid agonists and antagonists in humans not dependent on opioids. A retrospective analysis of data from six studies showed that healthy female volunteers experienced higher ratings of 'coasting (spaced out),' 'heavy or sluggish feeling' and 'dry mouth' in response to equivalent (10 mg/70 kg, intravenous) doses of morphine (Zacny, 2001). Moreover, healthy female volunteers not abusing drugs have been shown to experience significantly lower ratings of 'coasting (spaced out)', 'heavy or sluggish feeling' and 'dry mouth' in response to a painful stimulus during butorphanol administration compared to male volunteers (Zacny and Beckman, 2004). Meanwhile, in a study examining sex differences in pain and negative affect during psychological stress following administration of naltrexone (50 mg), naltrexone produced increases in cold-induced pain intensity and unpleasantness in women, but not men, following the stress-evoking discouragement task (Frew and Drummond, 2007).

Given that there are very limited data about differences in opiate withdrawal in the opioid-dependent population, this study retrospectively examined data from five naloxone discrimination studies (Oliveto et al., 1998, 2002, 2003a,b, 2004) in which opioid-maintained male and female volunteers were exposed to naloxone (0.15 mg/70 kg IM) and placebo in double-blind, counterbalanced procedures. The specific aim of this investigation was to examine whether sex and opioid maintenance dose differentially altered the response to naloxone compared to placebo in individuals on opioid maintenance. By examining how such factors might influence naloxone-induced responses, we hoped to gain a better understanding of individual characteristics related to physical dependence and withdrawal. This might provide useful information for improving relapse prevention in opioid-dependent humans.

2. Methods

2.1. Participants

Data from five human naloxone discrimination studies examining the effects of intramuscular naloxone and hydromorphone (Oliveto et al., 1998; $n=10$ [2 females, 8 males]; Study 1); intramuscular naloxone, butorphanol and nalbuphine (Oliveto et al., 2002; $n=19$ [7 females, 12 males]; Study 2); naloxone, clonidine and yohimbine (Oliveto et al., 2003a; $n=14$ [6 females, 8 males]; Study 3); naloxone and cycloserine (Oliveto et al., 2003b; $n=7$ [4 females, 3 males]; Study 4); and naloxone, isradipine and dextromethorphan (Oliveto et al., 2004; $n=17$ [7 females, 10 males]; Study 5) were used in the present report. Subjects for Study 1 and the first part of Study 2 were recruited via newspaper advertisements targeting opiate-dependent individuals currently not in treatment. The rest of the subjects (remainder in Study 2 and those from Studies 3 to 5) were recruited by flyers specifically targeting those on opioid maintenance in local opioid maintenance programs and by word of mouth. All gave written informed consent to participate in a study and were compensated monetarily for their participation. These studies had been approved by the Yale Human Investigations Committee and/or the West Haven VA CT Healthcare System Human Studies Subcommittee.

Data from subjects in each study were included in the analyses if the following conditions were met: 1) the subject had completed at least the first two study sessions (training phase) such that they had received naloxone during one and placebo during the other, respectively; and 2) if a subject participated in more than one study, only data from the first study was used for that subject (Oliveto et al., 1998, 2002, 2003a,b, 2004). Thus, data were available from 10 subjects in study 1 (Oliveto et al., 1998), 13 subjects from study 2 (Oliveto et al., 2002), 9 subjects from study 3 (Oliveto et al., 2003a), 2 subjects from study 4 (Oliveto et al., 2003b), and 13 subjects from study 5 (Oliveto et al., 2004). Overall, data from 47 subjects (15 female and 32 male, aged 24 to 51 years) were included in these analyses.

Each subject's eligibility was determined through a comprehensive evaluation that included complete physical, neurological, and psychiatric examinations; laboratory chemistry tests; and electrocardiogram. For all studies, subjects had to meet the following inclusion criteria: (1) opioid dependence, as evidenced by either opioid-positive urine plus signs of withdrawal on a Narcan challenge test (all subjects in study 1 and three subjects in study 2), or currently in a methadone maintenance program (10 subjects from study 2 and all subjects from studies 3–5) in good standing (i.e., compliant with program rules, including no illicit drug use); (2) no major cardiovascular, renal, endocrine, or hepatic disorder; (3) no current diagnosis of other drug or alcohol physical dependence (except nicotine); (4) no history of major psychiatric disorder (e.g., schizophrenia, bipolar disorder, major depression); (5) no pregnancy or plans to become pregnant, if female; (6) no present or recent use of over-the-counter or prescription psychoactive drug or drug that would have a significant interaction with the drugs to be tested; (7) negative urine toxicology for illicit drugs upon entering the study. Information regarding the phase of the menstrual cycle or the use of oral contraceptives was not recorded for the female participants.

All subjects in Study 1 and the first 3 subjects in Study 2 participated on an in-patient basis and provided confirmation of opioid dependence via urine toxicology screen and signs of withdrawal upon administration of naloxone in a Narcan challenge test (0.2 to 0.8 mg IM). They were subsequently stabilized on methadone, by a procedure described earlier (Oliveto et al., 1998, 2002). The remainder of the participants in Study 2 and all the patients in Studies 3 to 5 were already receiving stable methadone or *levo*-α-acetyl methadol (LAAM) maintenance doses between methadone dose equivalents of 25 to 120 mg/day at local programs and participated on an out-patient basis.

2.2. General procedure

All subjects participating in Study 1 and the first 3 subjects in Study 2 were admitted to the Treatment Research Unit at the Connecticut Mental Health Center, an inpatient facility for patients and research subjects with psychiatric and substance-abuse problems, once they met eligibility criteria. These subjects were stabilized on methadone (dose range: 25 to 45 mg/day) prior to the study proper and remained on the inpatient unit until the end of their participation (approximately 4–