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Precipitated opioid withdrawal across acute physical dependence induction methods

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Abstract

The phenomenon of acute opioid physical dependence (APD) is an established and well-characterized experimental model for studying the clinical phenomenon of physical dependence to opioids in humans. In this paradigm, an opioid withdrawal syndrome is elicited in non-opioid-dependent humans by the parenteral administration of naloxone (NX) following a single large dose of opioid agonist. Although induced by various opioids and NX administration schedules, lacking is a direct comparison of different induction protocols with respect to withdrawal severity. Using a crossover design, we compared withdrawal severity in four healthy male subjects pretreated with morphine (MS; 18 mg/70 kg im), MS (10 mg/70 kg iv) and hydromorphone (HM; 2 mg/70 kg) followed 2 or 6 h later with NX (10 mg/70 kg iv). Dependent measures included both physiological and subjective indicators of withdrawal. All opioid pretreatments reliably induced APD and repeated-measures analysis of variance (ANOVA) showed that both pattern and severity of precipitated withdrawal were similar across conditions. Thus, despite altering the pretreatment opioid and route of administration, all three APD protocols produced similar and reliable withdrawal symptoms in humans.

Keywords: Opioid; Physical dependence; Morphine; Hydromorphone; Naloxone; Precipitated withdrawal

1. Introduction

An important and well-described experimental model for studying the clinical phenomenon of physical dependence to opioids in humans is the induction of acute opioid physical dependence (APD). In this paradigm, healthy non-opioid-dependent subjects pretreated with a single large intramuscular (im) dose of μ-opioid agonist [typically 10–18 mg/70 kg morphine (MS)] and challenged 4–6 h later with a large parenteral dose of opioid antagonist [typically 10 mg/70 kg im or iv naloxone (NX)] show not only reversal of agonist effects but also evidence of a true opioid withdrawal syndrome (Azorlosa et al., 1994; Bickel et al., 1988; Higgins et al., 1992; Jones, 1979; Stitzer et al., 1991; Wright et al., 1991). The mechanisms underlying APD continue to be elucidated, and its relationship to physical dependence as it appears in chronically exposed individuals remains unclear, although there is evidence that its emergence is more profound following multiple opioid doses (Azorlosa et al., 1994; Kirby and Stitzer, 1993; Schulteis et al., 1997).

Consequent to extensive preclinical work describing the phenomenon of APD in animals (Gellert and Sparber, 1977; Kosersky et al., 1974; Martin and Eades, 1961, 1964; Smits, 1975; Wikler and Carter, 1953), Jones (1979) demonstrated its development in a small sample of normal human volunteers ($n=13$). In this work, the author reported precipitating significant physiological and subjective opioid abstinence symptomatology with intravenous (iv) doses of NX (10 mg/70 kg or 20 mg/70 kg) administered 24 h after a single intramuscular dose of MS (10 mg/70 kg or 15 mg/70 kg; Jones, 1979). Subsequent work, most notably from the laboratories of Stitzer and Bigelow, has specified the time course (June et al., 1995; Kirby et al., 1990), agonist/antagonist dose–response curves (Bickel et al., 1988; Heishman et al., 1989a; Higgins et al., 1992) and dosing interval parameters (Azorlosa et al., 1994; Heishman et al., 1989b, 1990; Kirby et al., 1990; Kirby and Stitzer, 1993) of APD induction. In general, it has been established that APD

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results in a true withdrawal syndrome, not simply the result of antagonism of opioid effects (Higgins et al., 1992), it follows pretreatment with pure μ agonists but not a mixed μκ agonist (Greenwald and Stitzer, 1998), its onset is delayed and duration of action is longer than other opioid agonist effects (June et al., 1995), it is precipitated within 5 min and peaks within 15 min of NX administration (Heishman et al., 1989a) and it occurs independently of the subjects' opioid abuse history (Azorlosa et al., 1994).

Across this impressive body of clinical work, the dependence-producing opioid agonist used has most commonly been MS administered by the intramuscular route of administration followed by NX 6 h later. Other opioids demonstrated to induce APD include the long-acting opioid intramuscular methadone (Wright et al., 1991; Stitzer et al., 1991) and the shorter-acting fentanyl and alfentanil administered intravenously (Greenwald et al., 1996). These data have established that the duration of APD is directly related to the half-life of the opioid administered.

The Greenwald et al. (1996) study, in particular, suggests that the phenomenon of APD can be examined within a shorter time frame and with agents of higher efficacy administered via the intravenous route. Early data indicate that behavioral indices of withdrawal severity vary with the dissociation constant and intrinsic activity of the pretreatment opioid (Martin et al., 1976; Stevens and Yaksh, 1989); thus, the equivalence of shorter APD induction protocols with high-potency opioids compared with traditional intramuscular MS induction protocols with respect to withdrawal severity remains to be described.

In an effort to compare the relative severity of APD withdrawal induced by opioids that vary with respect to route of administration and intrinsic activity, we used a crossover design and a small sample of normal healthy control subjects to compare the (1) relatively standard intramuscular MS pretreatment for APD induction with (2) MS administered by the intravenous route of administration and (3) higher-potency opioid hydromorphone (HM) also administered intravenously to directly compare their relative abilities to elicit APD in a given individual.

2. Methods

Using a quasi-experimental crossover design, four healthy male subjects underwent each of three APD induction protocols on two separate occasions. To minimize the risks associated with repeatedly exposing nonaddicted humans to opioids, the size of the sample was strictly limited by the Institutional Review Board. Repeat sessions were scheduled at least 14 days after the first session and consecutive, nonrepeated sessions were spaced at least 48 h apart, resulting in subjects undergoing ~1 session/week. Signs and symptoms produced by acute NX challenge (10 mg/70 kg iv) were described:

- 6 h after 18 mg/70 kg im MS
- 2 h after 10 mg/70 kg iv MS
- 2 h after 2 mg/70 kg iv HM

Doses of the intravenous medications were chosen to be relatively equianalgesic to intramuscular MS, and due to the earlier onset and peak action of opioids administered intravenously (i.e., Greenwald et al., 1996), the interval to NX (10 mg/70 kg iv) administration was shortened to 2 h. Order of testing sessions was restricted such that all subjects were exposed to the established intramuscular MS procedure on the first session; following this first session, subjects were exposed to the remaining five in random order.

2.1. Subjects

Participants were four healthy male volunteers recruited from the local university community; females were excluded due to menstrual cycle modulation of opioid response (Hoehe, 1988; Kitamura et al., 1996; Negus and Mello, 1999; Petraglia et al., 1986; Sarton et al., 2000) and because recent preclinical work suggests that APD is more robust in males (Kest et al., 2001). All received a medical screening that included a history and physical examination and were found in good health and deemed able to tolerate an opioid challenge. None reported taking any prescribed medication in the 30 days before screening, and all were nonsmokers. None reported a history of opioid dependence, addictive disease or chronic pain syndrome. Although each reported having taken a prescribed opioid at some point in his life, current opioid dependence was ruled out by history, screening urine toxicology and a single NX challenge (10 mg/70 kg iv) administered during a study training session (see below).

One Latino and three White subjects were between ages 24 and 35 (mean 30.8 years) and mean weight was 75.2 kg (range 74.1–81.8 kg). The study was approved by the Human Subjects Medical Institutional Review Board (University of California at Los Angeles), and each subject gave written informed consent before the start of the study. Subjects were financially compensated for their participation.

2.2. Procedures

All study sessions took place on a medically managed General Clinical Research Center (GCRC) to which study subjects were admitted as day outpatients. Participants were offered music or video entertainment while on the ward and were provided caffeine-free meals or snacks ad lib. For all study procedures occurring after opioid pretreatment, subjects reclined in a standard hospital bed. Before starting the study sessions, subjects partici-

pated in a practice session on the ward during which active NX was given following placebo to familiarize them with study procedures and rule out opioid dependency, NX sensitivity and independent NX effects on the dependent measures.

On arrival on the clinical ward for study sessions, an intravenous catheter was inserted in the subject's nondominant arm, and baseline measures were collected. After a 15-min rest period, the subject received the opioid pretreatment as described and was continuously monitored by nursing and study staff until the scheduled NX dose. Fifteen minutes before NX challenge (345-min postopioid pretreatment in the intramuscular MS condition and 105-min postopioid pretreatment in intravenous MS and intravenous HM conditions) and at 5 and 15 min post-NX infusion, measures consisting of heart rate (HR), respiratory rate (RR), pupillary diameter (PD) and subjective and objective measures of withdrawal were collected. Subjects were not discharged until deemed medically stable and free of opioid effects. Thus, the total length of experimental sessions was between 4 and 9 h depending on condition.

Hospital formulary MS, HM and NX were used, with doses adjusted for body weight. Pretreatment opioids (MS and HM) were prepared and administered by an unblinded member of the GCRC nursing staff by either intramuscular injection (MS) or slow intravenous push (MS and HM) via a venous access device. Intravenous doses were diluted to a constant volume of 2.0 ml, and data collection staff and subject were blinded to drug administration. NX dose was kept constant at 10 mg/70 kg and supplied to the nursing staff in prepackaged syringes for slow (over 1 min) intravenous push administration.

2.3. Measures

APD responses were measured on physiological and subjective domains. In addition to HR and RR, PD was photographed with a clear-lens adapted Polaroid camera at constant room light for evidence of sympathetic stimulation induced by NX challenge. Subjective and objective withdrawal symptoms were measured on 15-item, 10-point scales ranging from 0 (*symptom absent*) to 9 (*severe symptom*; Heishman et al., 1989a) by both the subject and a trained blinded research assistant. The extent to which the following symptoms typical of opioid withdrawal were present were rated: muscle cramps, painful joints, yawning, hot or cold feelings, upset stomach, irritability, runny nose, sneezing, watery eyes, restlessness, abdominal cramps, backache, chills or gooseflesh, bothered by noises and clammy and damp skin.

2.4. Data analysis

Change scores from baseline were calculated for the physiological variables, and total scores were calculated for the withdrawal scales at 5 and 15 min post-NX administration for descriptive analysis. Correlations among change scores of HR, RR, PD and total subjective and objective opioid withdrawal scores on repeated induction sessions were found to be good to excellent, and the values were averaged before analysis. Because the values at the 5 and 15 min post-NX time points were similar, these were also averaged. Next, we constructed a series of repeated-measures analysis of variance (ANOVA) models for the physiological change scores and on the withdrawal scores. These ANOVA models contained one main effect (type of induction protocol) as well as the subject effect to account for the repeated observations. Ratings on individual items on the subjective and objective withdrawal scales at the post-15-min time point were also examined and compared using the same analytical techniques. All analyses were run using SPlus statistical software.

3. Results

As Table 1 shows, symptoms of APD were evident in all induction conditions at both 5 and 15 min following NX administration. Improved withdrawal symptom severity at the 15-min time point relative to 5 min was evident across conditions for subjective and objective reports but only for the intravenous MS condition on physiological measures. Evident of the sympathetic nervous system response to the NX challenge, HR, RR and PD all increased. In all cases, total subjective withdrawal scores were higher than those noted by the trained objective observer.

The repeated-measures ANOVA analysis on averaged 5 and 15 min measures reveals no difference between APD induction techniques on physiological responses and subjective withdrawal scale scores (see Table 1). A difference (P=.04) was noted on the objective withdrawal scale score.

Table 1
APD responses by induction protocol

Time post-NX		Intramuscular MS		Intravenous MS		Intravenous HM		*P*value[a] (*F*) (*df*)
		5 min	15 min	5 min	15 min	5 min	15 min	
Physiological responses[b]								
HR/min	Mean	5.88	6.75	2.50	−0.62	5.25	5.25	0.13
	S.D.	4.3	5.4	1.3	0.9	5.0	10.2	2.64 [2]
PD (cm)	Mean	0.26	0.22	0.15	0.14	0.19	0.20	0.25
	S.D.	0.1	0.1	0.1	0.1	0.1	0.1	1.64 [2]
RR/min	Mean	2.00	3.75	1.86	1.00	2.13	2.50	0.61
	S.D.	1.8	1.6	2.7	1.8	3.3	3.0	0.52 [2]
Withdrawal symptoms[c]								
Subjective report	Mean	37.00	32.38	37.00	26.75	31.88	24.38	0.85
	S.D.	16.2	22.8	18.1	32.5	22.9	18.5	0.16 [2]
Objective report	Mean	21.63	20.50	13.88	10.13	21.13	13.13	0.04
	S.D.	7.2	4.6	8.1	6.0	5.3	5.0	5.2 [2]

[a] *P*'s based on averaged 5 and 15 min time points.
[b] Change scores from baseline.
[c] Total scale scores.

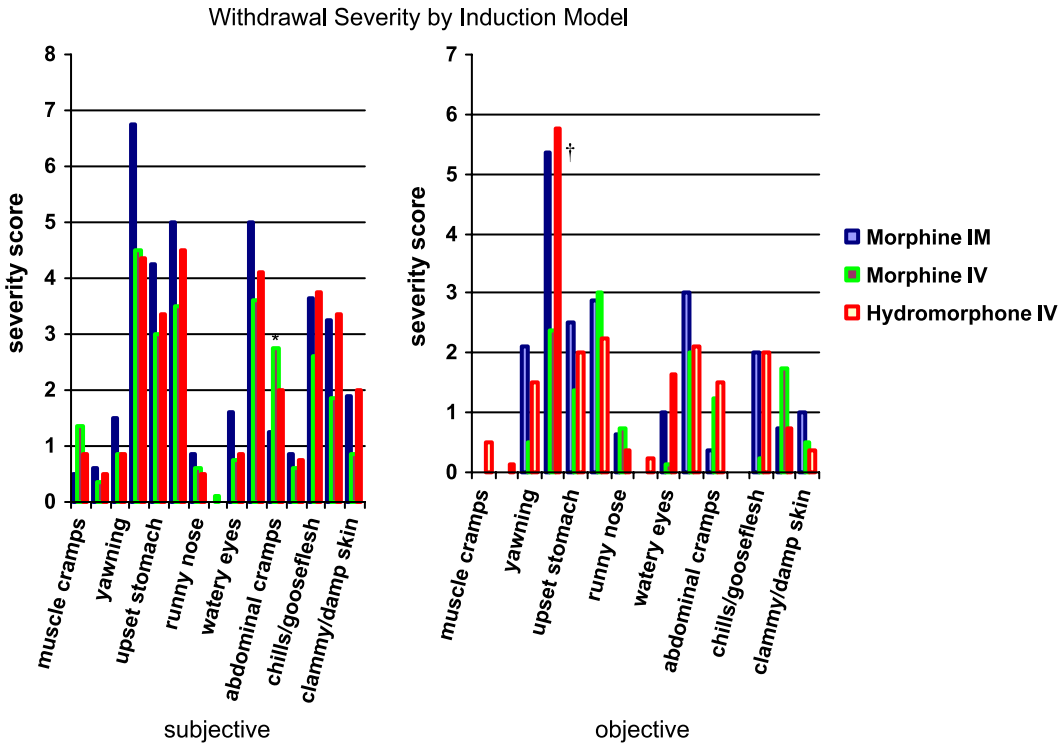

Fig. 1. Mean opioid withdrawal symptoms scores by APD induction protocol. * P=.046, † P=.017.

Examining individual items on the subjective and objective withdrawal scales at the 15-min post-NX time point reveals similar patterns of withdrawal symptom severity across induction conditions (see Fig. 1). "Hot or cold feelings" was the most severe symptom reported by both subjects and observers followed by "irritability" and "restlessness" for all induction conditions. At the same time point, repeated-measures analysis on the objective withdrawal scale ratings showed that only "hot or cold feelings" significantly differed ($P<.02$) with the intramuscular MS and intravenous HM conditions, producing more severe symptoms than the intravenous MS condition. Differences in subjective withdrawal severity achieved statistical significance ($P<.05$) for the symptom "abdominal cramps," with intravenous MS producing the most severe cramping and intramuscular MS the least severe cramping.

4. Discussion

APD was reliably induced in normal control subjects 6 h following agonist pretreatments with intramuscular MS and 2 h after treatment with intravenous MS and intravenous HM, respectively. Correlations between repeated sessions were moderate to high, indicating that the test–retest reliability of the APD procedure, regardless of pretreatment opioid condition, is good.

The magnitude of withdrawal responses to intramuscular MS was quite similar to those previously reported using similar induction protocols. Published NX-induced changes in RR range from 1.7 to 4 breaths/min within 15–30 min of NX administration (Bickel et al., 1988; Heishman et al., 1989a,b; Kirby et al., 1990), replicating our finding of changes of 2–3.75 breaths/min at 5 and 15 min post-NX administration. Similarly, our findings of an increase in PD by 0.22–0.26 cm fall just above reported ranges of 0.13–0.21 cm (Bickel et al., 1988; Heishman et al., 1989a,b, 1990; Higgins et al., 1992; Kirby et al., 1990) and our HR changes (5.9–6.8 bpm) just above the 4 bpm reported by Heishman et al. (1989a). Using the same subjective withdrawal scale as used in the present study, Heishman et al. (1989b) and June et al. (1995) reported total withdrawal scores ranging from 30 to 40; subjects in our study reported average scores of 37 at 5 min post-NX and 32.4 at 15 min post-NX.

The only dependent measures on which the induction protocols differed were one subjective withdrawal symptom (abdominal cramps) and one objective withdrawal symptom (hot/cold feelings), and the differences were not consistent with respect to induction technique. Intravenous MS resulted in the most severe abdominal cramps yet the least severe hot/cold feelings. It is unlikely that these differences are attributable to anything other than random error.

Apparently, differential effects of induction methods might have been detected if timing of the NX challenge had been closer to intravenous pretreatment agonist administration, yet Greenwald et al. (1996) elicited APD withdrawal effects with NX challenge 2 h following the short-acting opioid intravenous fentanyl. Further, it has been suggested that APD can be induced for up to four half-lives

of the pretreatment opioid (Greenwald et al., 1996); the 2-h time point of NX administration is well within this time period for both HM ($T_{1/2}$ = 2.6 h) and MS ($T_{1/2}$ = 1.5–2 h). Alternatively, the data of June et al. (1995) show that the most robust precipitated withdrawal symptoms occur 6–12 h following agonist administration, suggesting that perhaps differential effects would be noted had the interval to NX administration been longer.

An alternate explanation for the lack of differences among APD responses is the use of the intravenous route of NX administration in all three induction protocols. Intravenous NX represents a change from the standard intramuscular MS protocol used in the laboratories of Stitzer and colleagues in which NX was administered intramuscularly, although the intravenous route is the administration route originally used by Jones (1979) in the first published exploration of human APD. Apparently, with intravenous administration, NX effectively floods opioid receptor systems to the extent that APD is maximally expressed regardless of pretreatment induction protocol. Yet, in that APD responses following intramuscular MS pretreatment noted in the current study are remarkably similar to those published using the same dose of intramuscular NX following intramuscular MS, this explanation seems unlikely. The specific route of NX administration does not appear to differentially affect APD induction.

Preclinical data provide indirect evidence that the rate onset of drug effect (i.e., intramuscular vs. intravenous administration) may have less an effect on APD severity than does the total amount of opioid administered. Rats infused with MS at differing rates did not differ in expression of APD responses, whereas the total amount of MS received predicted APD severity regardless of infusion rate (Kishioka et al., 1995, 1996). In this direct comparison of APD induction methods, these pilot data suggest that APD is similarly and reliably induced using different opioid agonists and routes of administration.

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