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The effects of a cold-water stimulus on butorphanol effects in males and females

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Abstract

Using a crossover, randomized, double-blind, cumulative-dosing procedure, we examined whether a painful stimulus modulated subjective and psychomotor effects of butorphanol in eight male and eight female volunteers. During each session, volunteers received four intravenous injections of either butorphanol (0, 0.5, 1, and 2 mg/70 kg) or saline (placebo) at hourly intervals. Saline and butorphanol were tested in two conditions, forearm immersion 30 min after each injection into either 2 or 37 °C water. During the 180-s immersion, volunteers completed a visual analog scale (VAS), psychomotor test, and pain ratings. VAS ratings of "Coasting ('spaced out')", "heavy or sluggish feeling," and "sleepy" were lower in the 2 °C than in the 37 °C condition during butorphanol administration, but only in females. Modulation by a painful stimulus of sleepy ratings was confined to the third immersion (i.e., a dose effect). The cold-water stimulus significantly decreased butorphanol-induced impairment during the third immersion for males, and females showed a similar trend. Overall, pain ratings were higher in females, and although not significant, males reported a greater degree of analgesia. The differences in pain ratings and degree of analgesia between the sexes are discussed as a possible mechanism for the sex differences in modulatory effects.

Keywords: Opioid; Butorphanol; Pain; Subjective; Psychomotor; Human

1. Introduction

There have been a number of case reports and studies that have indicated that several effects of opioids are modulated by painful stimuli. For example, case reports as well as laboratory studies have demonstrated that a common effect of opioids, respiratory depression or parameters that contribute to that state, are attenuated when human patients or volunteers are in pain (Wells et al., 1984; Borgbjerg et al., 1996; Quevedo and Walsh, 1999). Self-administration of opioids occurs at a higher rate in animals that are subjected to a painful stimulus than animals that are not (e.g., Dib and Duclaux, 1982; Shaham and Stewart, 1994; Colpaert et al., 2001). A number of studies assessing self-administered opioids in patients via the patient-controlled analgesia (PCA) delivery system have shown that self-administration frequency is directly related to pain, with more use of the PCA pump when pain is higher, than when it is abating (e.g., Graves et al., 1985; Berman et al., 1990; Gil et al., 1990). In non-drug-abusing volunteers, fentanyl choice was higher when volunteers knew they were going to be subjected to a painful stimulus, relative to a nonpainful stimulus (Zacny et al., 1996). In several animal studies, pain decreased the rate at which opioid tolerance developed (Rahman et al., 1993, 1994; Vaccarino et al., 1993; Ho et al., 1999; Bardin et al., 2000), and this phenomenon has also been noted in patients suffering from chronic pain (Twycross, 1974; Portenoy and Foley, 1986). Thus, with the exception of opioid self-administration, pain appears to act as a "natural antagonist" to some opioid effects (cf. Hanks and Twycross, 1984).

We asked in a previous study whether this "antagonist" effect applied to subjective and psychomotor/cognitive effects of opioids. There was a study conducted over 60 years ago suggesting this might be the case. In that study

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(Wolff et al., 1940), the three experimenters served as participants and assessed their own emotional state when receiving morphine (15 mg im) while in pain. Ice-cold water and ischemia produced by sustained inflation of a blood pressure cuff served as painful stimuli. The authors noted that pain reduced the intensity and duration of such "psychological effects" of morphine as freedom from anxiety, contentment, and relaxation (p. 675). In another study in chronic pain patients, controlled-release morphine led to a significant reduction in pain, without patients reporting sedation. The authors suggested that the pain that was still present had an arousing effect that prevented morphine-induced sedation (Lorenz et al., 1997). In our previous study using a crossover design, healthy volunteers were injected intravenously with saline, morphine (10 mg/70 kg), and butorphanol (2 mg/70 kg) and at fixed intervals after the injection had to immerse their nondominant forearm in 2 or 37 °C water (Conley et al., 1997). During each 180-s immersion, participants filled out a visual analog scale (VAS) of subjective effects and completed the Digit Symbol Substitution Test (DSST). Several subjective effects of morphine were attenuated in the 2 °C condition relative to the 37 °C condition, including ratings of "Coasting ('spaced out')" "lightheaded," "high," and "sleepy." However, subjective and psychomotor-impairing effects of butorphanol were not attenuated by the painful stimulus. One potential reason is that the subjective and psychomotor effects of mixed-action agonists, such as butorphanol, may be insensitive to a painful stimulus. However, another plausible explanation is that we tested a dose of butorphanol that was perhaps too high, and at lower doses, a modulatory effect might have been observed. This formed the basis of our present study.

2. Methods

2.1. Participants

Participants were recruited from the surrounding community via newspaper and bulletin board advertisements. Candidates who met screening criteria (i.e., 21–39 years old, fluent in English, had a high school diploma or its equivalent, within 20% of ideal body weight, reporting some level of current recreational drug use, and no current medical problems) were scheduled for a screening interview. Minimum level of current recreational drug usage was defined as consumption of at least three alcoholic drinks a month or some (e.g., one joint/week) but not daily use of marijuana. Candidates with any history of significant psychiatric disorders or substance use disorder (American Psychiatric Association, 1994), except for tobacco dependence, were excluded. An anesthesiologist performed a medical history and physical examination, and a resting electrocardiogram was performed. Our institutional review board approved the studies. Written informed consent was obtained from participants before the first session. In the consent form, participants were told that the drugs they would receive in the experiment may come from one or more of the following classes of drugs in intravenous form: sedative, stimulant, general anesthetic (at subanesthetic doses), opiate, alcohol, or placebo. Participants were paid for their participation upon study completion.

Eight male [mean age (range) = 25.9 (21–33) years] and eight female [mean age (range) = 26.4 (22–31) years] healthy volunteers completed the study. Menstrual cycle phase was not assessed in this study, but five females were on oral contraceptives. The participants who completed the study reported consuming an average of two alcoholic drinks per week (range = 0.25–5 drinks). Three participants currently smoked marijuana (average of 1.1 joints per week). Four volunteers were cigarette smokers but none reported smoking more than five cigarettes per day. Eight participants reported use of prescribed opiates in their lifetime (Vicodin, Darvocet, morphine) and four more had been prescribed "painkillers," the classes or names of which they could not report. Three participants reported using opiates recreationally on less than five occasions [codeine, opium, heroin (smoked), Percocet].

2.2. Design

A randomized, placebo-controlled, double-blind, crossover trial was conducted. Participants participated in four experimental sessions, scheduled at least 1 week apart. Sessions were approximately 7.5 h in duration. Saline was injected intravenously first during each session, then saline or increasing doses of butorphanol were administered every hour for the next 3 h. Absolute doses of butorphanol administered were 0, 0.5, 1.0, and 2.0 mg/70 kg resulting in cumulative doses of 0, 0.5, 1.5, and 3.5 mg/70 kg. Doses were injected over a period of 30 s, and the total volume of each injection was 5 ml, with saline as the vehicle. The largest absolute amount of butorphanol injected, 2 mg, was a dose that typically would be prescribed for postoperative pain relief, and the smaller absolute doses were one half and one fourth of this dose (Reisine and Pasternak, 1996). To maintain the double-blind nature of the study, the drugs were drawn up by one anesthetist and injected by another. Although both the experimenter and the anesthetist injecting the drug were aware of the drugs under study, they were blind to the drug condition during each session.

During two of the sessions, participants immersed their nondominant forearm in 2 °C water (painful stimulus) 30 min after each of the four injections. In the other two sessions, participants immersed their nondominant forearm in 37 °C water (nonpainful stimulus, control) at the same times. The study was designed so that butorphanol and saline would be experienced under both temperature conditions. During the immersions, pain ratings, mood, and psychomotor performance were assessed. Volunteers used

their dominant hand to complete these paper-and-pencil assessments. In addition, at set time points after each injection, a nonimmersion testing battery that assessed subjective, psychomotor, and physiologic measures was administered. For brevity's sake, and because the tests from the battery yielded measures that were secondary variables of interest to this study, the description and results from the battery will not be discussed.

2.3. Forearm water immersion

The water-immersion apparatus consisted of a picnic cooler (48-qt Coleman cooler; Wichita, KS) divided into two compartments by a wire screen. A cradle for the participant's forearm was positioned in one side of the compartment, which allowed the participant to rest the forearm while immersing it into the water. Each immersion of the nondominant arm lasted 180 s at which point the arm was removed from the water, dried with a towel, and placed in a bath of lukewarm water for an additional 180 s. The cold-water temperature was 2 °C and the warm-water temperature was 37 °C. The cold-water temperature was achieved by adding crushed ice to one side of the compartment. This cold-water immersion has been used in numerous other studies to induce pain, and is known as the cold pressor test. The cold pressor test is a well-established model of producing tonic pain in humans (Chen et al., 1989).

2.4. Sessions

The experiment took place in a departmental laboratory. Toxicology screening and breath intoximeter readings ensured the absence of drugs and alcohol before experimental sessions. Blood-alcohol levels were measured with a breath intoximeter, and negative pregnancy results for females were required before each session. Participants reclined on a hospital bed in a semirecumbent position (thus, movement in the present study was minimal). An anesthetist inserted an angiocatheter into a forearm or hand vein on the participant's dominant arm and a pulse oximeter was placed on one finger of the participant's dominant hand. Heart rate and arterial oxygen (O_2) saturation were continuously monitored throughout the session. Immediately before the first injection, participants were told, "The injection you are about to receive may or may not contain a drug," and the anesthetist injected saline through the angiocatheter. A timer was started immediately after the 30-s injection (the first injection was considered to be the 0-min time point). Participants performed the water-immersion test 30 min after each injection; the immersion time points were 30, 90, 150, and 210 min after the first injection. One hour after the first (saline) injection, participants were told again, "The injection you are about to receive may or may not contain a drug," and the anesthetist injected the smallest drug dose (or saline during the placebo session). Participants received two more injections in this way, with the medium and largest dose (or saline) being injected 2 and 3 h, respectively, following the first saline injection.

Between testing periods, participants were allowed to engage in sedentary leisure activities, such as reading, listening to music, or watching television, but work and school-related activities were not allowed. At the end of the session, the anesthetist removed the catheter, provided that they judged the participant fit for discharge and the participant's vital signs were similar to those at baseline (within 20%). Participants were transported to their home via a transportation service with instructions not to engage in certain activities (e.g., driving, cooking, operating machinery, and drinking alcohol) for 12 h following the session. Payment for study participation was made at a debriefing session at least 24 h after the last experimental session.

2.5. Dependent measures

During the 180-s forearm immersion, participants provided written ratings at 10, 30, 100, and 170 s in response to the following questions: "How painful is it?" and "How much does it bother you?" (0 = *not painful/bothersome at all* and 10 = *the most painful/bothersome feeling imaginable*). The average pain intensity and bothersome ratings collapsed across the four time points (i.e., 10, 30, 100, and 170 s) served as dependent measures.

Within each immersion at the 40-s time point, participants also completed a paper-and-pencil VAS containing the following 14 items: "stimulated (energetic)," "high ('drug' high)," "lightheaded," "confused," "elated (very happy)," "nauseous," "coasting ('spaced out')," "feel good," "feel bad," "having unpleasant bodily sensations," "heavy or sluggish feeling," "difficulty concentrating," "sleepy (drowsy, tired)," and "floating." The same items had been used in the Conley et al. (1997) study, with the exception of "floating." Participants were instructed to place a vertical tick mark on each line indicating how they felt at the moment, ranging from "not at all" (0 mm) to "extremely" (100 mm). At the 110-s time point, participants completed a 60-s DSST. This paper-and-pencil test required the participant to replace digits with corresponding symbols according to a digit–symbol code listed on the top of the paper (Wechsler, 1958). The dependent measure was number of symbols drawn correctly. Different forms of the test (i.e., different symbol–digit codes) were used each time the test was presented to the participant in a session. The DSST assesses a number of different functions, including perception, decision making, and motor abilities (Wetherell, 1996).

2.6. Data analysis

Repeated-measures analysis of variance (ANOVA) was used for statistical treatment of the data. F values were considered significant for $P < .05$ with adjustments of with-

in-factors degrees of freedom (Huynh–Feldt) to protect against violations of symmetry. Factors used in the analysis were drug (two levels: saline and butorphanol), temperature (two levels: 2 and 37 °C), immersion trial (essentially corresponding to dose, four levels: 30 [30 min after Injection 1], 90 [30 min after Injection 2], etc.), and sex (male and female). In analyzing pain intensity and bothersome ratings, factors were drug, immersion trial, and sex. The 37 °C data were excluded because pain ratings were virtually at 0. Because the purpose of the present study was to examine modulating effects of pain, rather than sex differences, we did not power the study to examine potential effects of sex. Nevertheless, we included sex as a factor because the total sample size was evenly divided by sex. Tukey post hoc testing was done when appropriate.

3. Results

3.1. Subjective effects

Modulatory effects of pain (i.e., cold-water stimulus) on butorphanol effects would be manifested by either significant Drug × Temperature or Drug × Temperature × Immersion Trial (dose) interactions. There were several butorphanol effects modulated by temperature, but in most of these cases there were also Sex × Drug × Temperature or Sex × Drug × Temperature × Immersion Trial interactions. Tukey post hoc testing on these and other effects in which higher order interactions involving sex were obtained revealed that effects were observed in one of the sexes but not the other. Table 1 shows mean ratings of VAS adjectives in which there was a significant Sex × Drug × Temperature interaction, and Fig. 1 shows the mean ratings of one of the two VAS adjectives in which a Sex × Drug × Temperature × Immer-Immersion Trial was obtained.

On ratings of coasting (spaced-out) and heavy or sluggish feeling, females but not males showed significantly lower mean ratings in the butorphanol 2 °C condition than in the butorphanol 37 °C condition (Table 1). The table also shows that mean ratings of coasting (spaced-out) were significantly higher in females than in males in the butorphanol 37 °C condition, and mean ratings of heavy or sluggish feeling were significantly higher in females than in males in both the butorphanol 37 °C and the butorphanol 2 °C conditions. Although there was a significant Sex × Drug × Temperature interaction on the rating of lightheaded, post hoc testing did not reveal any modulatory effects of sex. Males, but not females, had significantly lower mean ratings of having unpleasant bodily sensations in the butorphanol 2 °C condition than in the saline 2 °C condition. Females had significantly higher ratings than did males on this VAS measure in both the saline 2 °C and the butorphanol 2 °C conditions.

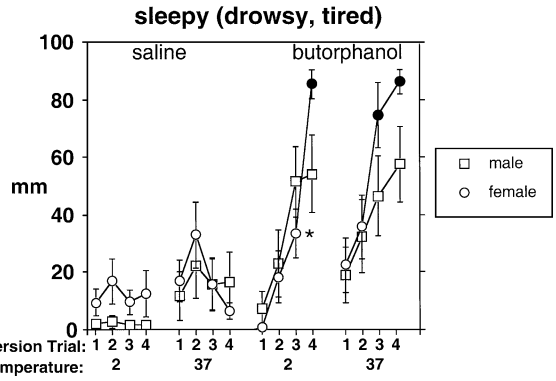

Fig. 1. Effects of sex, drug, temperature, and immersion trial on mean ratings of sleepy (drowsy, tired). Ratings are expressed in millimeters. Brackets indicate S.E. Immersion trial and water temperature are on the *x*-axis. Each of the immersions was done 30 min following an injection, which corresponds to 30 (Immersion 1), 90 (Immersion 2), 150 (Immersion 3), and 210 (Immersion 4) min after the first injection. On the left side of the graph are mean ratings in the saline conditions; on the right side are mean ratings in the butorphanol conditions. Males are represented by squares and females are represented by circles. Solid circles indicate that females at a given immersion trial had significantly higher ratings than did males. The asterisk represents a significant difference in ratings between the 2 and 37 °C conditions in females.

Table 1
Mean ratings (S.E.) of VAS adjectives in which significant Sex × Drug × Temperature interactions were obtained

	Female				Male			
	Saline		Butorphanol		Saline		Butorphanol	
	2 °C	37 °C	2 °C	37 °C	2 °C	37 °C	2 °C	37 °C
Coasting	6.8 (2.4)	5.0 (2.3)	27.2 (6.1)[a]	36.6 (5.9)[b]	2.6 (1.0)	3.8 (2.0)	21.4 (5.3)	23.5 (5.9)
Heavy or sluggish feeling	10.7 (2.4)	11.2 (2.9)	34.4 (6.2)[a,c]	51.9 (6.7)[b]	2.8 (1.0)	6.9 (2.4)	22.8 (5.7)	27.6 (5.8)
Lightheaded	8.8 (3.0)	3.5 (2.0)	26.1 (5.4)	32.8 (5.9)	2.5 (0.8)	3.7 (2.1)	24.7 (5.5)	25.7 (6.2)
Having unpleasant bodily sensations	65.6[d] (4.5)	9.4 (4.2)	65.1 (4.7)[e]	9.8 (3.2)	47.8 (6.0)	7.6 (2.6)	29.6 (5.6)[f]	9.0 (3.3)

[a] Females had significantly lower ratings in the butorphanol 2 °C condition than in the butorphanol 37 °C condition.
[b] Females had significantly higher ratings than males in the butorphanol 37 °C condition.
[c] Females had significantly higher ratings than males in the butorphanol 2 °C condition.
[d] Females had significantly higher ratings than males in the saline 2 °C condition.
[e] Females had significantly higher ratings than males in the butorphanol 2 °C condition.
[f] Males had significantly lower ratings in the butorphanol 2 °C condition than in the saline 2 °C condition.

Fig. 1 shows mean ratings of sleepy (drowsy, tired) as a function of sex, temperature, and immersion trial. Females had significantly lower mean ratings of sleepy (drowsy, tired) during the third immersion in the butorphanol 2 °C condition than in the third immersion of the butorphanol 37 °C condition. Females also had significantly higher ratings of sleepy (drowsy, tired) ratings than did males in both the butorphanol 2 °C (limited to fourth immersion) and the butorphanol 37 °C (limited to third and fourth immersion) conditions. There were baseline (control) differences in the butorphanol condition with both males and females showing higher ratings in the 37 °C condition than in the 2 °C condition; because of this, a change score analysis in which drug was subtracted from saline to compensate for this difference was conducted. The change score analysis yielded results similar to those described above (i.e., significant modulatory effect of sex during the third immersion with females having lower ratings in the 2 °C condition than in the 37 °C condition). ''Stimulated'' ratings showed a statistically significant Sex × Drug × Temperature × Immersion Trial interaction (data not shown), but the only significant difference was observed during the first immersion, with males showing significantly higher mean ratings in the 2 °C condition than in the 37 °C condition. This was not considered a true interaction involving the factor drug though, because the first immersion in both the saline and butorphanol conditions had been preceded by saline.

A Drug × Temperature × Immersion Trial interaction was found on the rating of feel bad ($P<.03$). Post hoc testing, though, revealed that regardless of drug and immersion trial (dose), mean feel bad ratings were significantly lower when the water temperature was 37 °C than when it was 2 °C.

There were a number of significant Drug × Immersion Trial interactions: butorphanol increased mean ratings of coasting, confused, difficulty concentrating, floating, heavy or sluggish feeling, high, lightheaded, sleepy (drowsy, tired), and decreased mean ratings of stimulated. Post hoc testing revealed that most of the Drug × Trial Immersion effects were limited to the third and fourth immersions (i.e., after cumulative doses of 1.5 or 3.5 mg butorphanol). There was one significant drug effect (i.e., not affected by trial immersion): mean ratings of elated (very happy) were increased by butorphanol. Two subjective effects ratings, feel good and nauseous, were not affected by butorphanol.

3.2. DSST performance

There was a significant Sex × Drug × Temperature × Immersion Trial interaction ($P<.02$) on number of symbols drawn correctly on the DSST. Males drew 5.8 more symbols correctly in the butorphanol 2 °C condition than in the butorphanol 37 °C condition during the third immersion. Females showed a similar effect, but it failed to reach significance by post hoc testing: they drew 5.4 more symbols correctly in the butorphanol 2 °C condition than in the butorphanol 37 °C condition. A significant Drug × Immersion Trial effect ($P<.001$) was significant, with worse performance in the butorphanol condition than in the saline condition at the third and fourth immersions.

3.3. Pain ratings

Significant Drug × Immersion Trial interactions were obtained with pain intensity ($P<.02$) and bothersome ($P<.01$) ratings. Post hoc testing revealed that both pain ratings were significantly reduced during the third and fourth immersions in the butorphanol condition, relative to the saline condition. Sex did not significantly modulate this effect. However, a significant Sex × Immersion Trial effect ($P<.04$) was obtained on pain intensity ratings. Post hoc testing revealed that at all four immersions, females reported higher ratings than did males. Fig. 2 displays average pain intensity ratings in the saline and butorphanol conditions as a function of both sex and immersion trial. Although not statistically significant, pain ratings were reduced to a greater extent in the butorphanol condition in males than in females. The mean drop in pain intensity ratings from the first to the fourth immersion in the butorphanol condition was 1.9 for males and 0.6 for females.

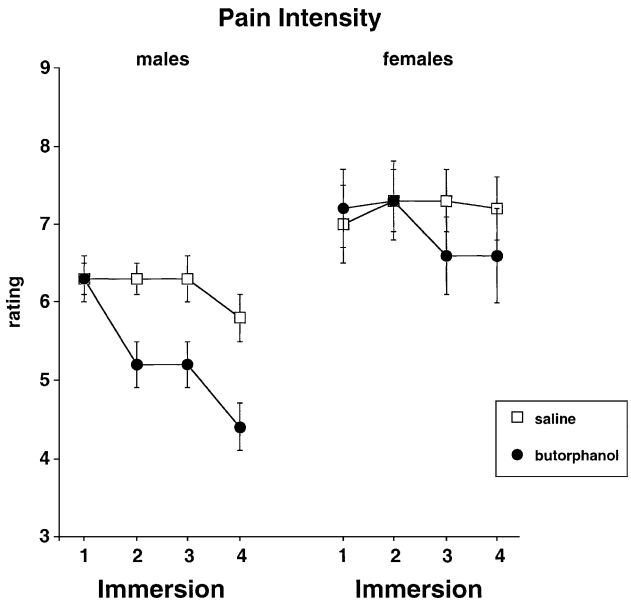

Fig. 2. Effects of sex, drug, and immersion on ratings of pain intensity. Data are shown only from the 2 °C condition. Open squares represent the saline condition and solid circles represent the butorphanol condition. Each of the immersions was done 30 min following an injection, which corresponds to 30 (Immersion 1), 90 (Immersion 2), 150 (Immersion 3), and 210 (Immersion 4) min after the first injection. Range of pain ratings is 0–10 (0 = *not painful at all*; 10 = *the most painful feeling imaginable*). Brackets indicate S.E.

4. Discussion

The intent of this study was to determine whether and to what degree butorphanol subjective and psychomotor effects, at one or more doses, were modulated by a painful stimulus. Indeed, several prototypic subjective effects of butorphanol [coasting (spaced-out), heavy or sluggish feeling, and sleepy (drowsy, tired)] were lower in the 2 °C condition than in the 37 °C condition. However, we unexpectedly found that the modulation of these effects was sex dependent, with females showing the effect. Although the study was not powered to determine if sex modulated the effects of a painful stimulus on butorphanol effects, significant sex effects were obtained, in part, because most females showed the effect (pain modulation of several subjective effects of butorphanol) and most males did not.

The present study replicated results of our earlier study examining the effects of a painful stimulus on subjective and psychomotor effects of butorphanol and morphine (Conley et al., 1997). Essentially, that study was done in males, in that 12 of the 13 participants were male. Males in that study had lower pain ratings after butorphanol administration, relative to saline, in the 2 °C condition. Males also reported a similar magnitude of subjective effects across the temperature manipulation. The temperatures used in that study were identical to those used in the present study. What is interesting though is that in the Conley et al. (1997) study, morphine produced the same degree of analgesia as did butorphanol, but in this case, males did report lower ratings on several subjective effects in the 2 °C condition than in the 37 °C condition. The Conley et al. (1997) study would suggest that males are sensitive to the effects of a painful stimulus on morphine effects, but relatively insensitive to the effects of a painful stimulus on butorphanol effects. This latter finding was also obtained in the present study. Therefore, in two different studies with differing methodologies, we were largely unable to demonstrate that males are sensitive to the effects of pain on butorphanol effects. The only subjective effect of butorphanol that was modulated by a painful stimulus in males in both studies was having unpleasant bodily sensations. What was different about the present study from the Conley et al. (1997) study was that an equal number of males and females were used, so that the effects of butorphanol could be studied in females. In this study, modulation of subjective effects of butorphanol by a painful stimulus did occur, but primarily only in females. Taking both studies into account, we would suggest that sex of the participant might play a role in whether the subjective effects of butorphanol are modulated by a painful stimulus.

One reason that females may have shown a modulatory effect of pain on butorphanol effects but males did not is that males reported lower pain intensity ratings and, although not statistically significant, greater analgesia than females (Fig. 2). If the lesser pain ratings by males truly reflect less pain, then one should not be surprised that females showed more modulation by pain than males (i.e., the putative modulating stimulus was more intense for females than for males). The higher pain ratings in the present study are consistent with other studies that show that females have lower pain thresholds than males (e.g., Fillingim and Maixner, 1995; Berkley, 1997; Riley et al., 1998). Sex differences in analgesia and antinociception have been reported in numerous opioid studies (cf. Miaskowsi and Levine, 1999; Kest et al., 2000; Craft, 2003; Pleym et al., 2003). In the only study to our knowledge that examined sex differences in degree of analgesia from butorphanol, using an impacted third molar tooth extraction as the painful stimulus, butorphanol analgesic effects differed between males and females (Gear et al., 1996). In that study, however, females reported a more prolonged duration of pain relief than did males. The reason for the discrepancy with our findings showing greater analgesia in males, although not a statistically significant effect, is not clear. One possible reason is type of pain (tooth extraction vs. cold water). Obviously, further research is needed using different pain assays to determine under what conditions and in what direction sex differences occur to the analgesic effects of butorphanol.

Psychomotor performance (number of symbols drawn correctly on the DSST) was less impaired in the butorphanol 2 °C condition than in the 37 °C condition in males, as confirmed by post hoc testing. However, given the fact that females showed almost the same magnitude of effect, it would be premature to conclude that pain modulation of impairing effects of butorphanol is sex dependent.

In summary, the present study found sex differences in the modulating effects of pain on butorphanol effects in healthy, young, non-drug-abusing volunteers, although it was not designed (powered) to assess such effects. Given more participants, more statistically significant effects might have been observed, as well as more robust sex differences [e.g., more immersion (dose)-related effects]. Further research is needed in order to draw more definitive conclusions on the role of sex in pain modulation of opioid effects. Besides replicating the present study using more participants, another experiment should assess whether the modulating effects of pain on morphine subjective effects observed by Conley et al. (1997), using predominantly male volunteers, also occur in female volunteers. Finally, it would be interesting to determine if other stimuli besides pain that induce sympathetic activation [social stress (e.g., Schommer et al., 2003) and exercise (e.g., Brys et al., 2003)] would have a modulating influence on opioid effects.

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