Effects of High-Dose Intravenous Buprenorphine in Experienced Opioid Abusers

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Abstract: Sublingual buprenorphine, a long-acting, partial mu-opioid agonist, is as effective as methadone in the treatment of heroin dependence, with a better safety profile due to its antagonist activity. However, the safety of therapeutic doses (8 to 16 mg) that might be diverted for intravenous (IV) use has not been demonstrated. To evaluate the safety and possible ceiling effects of buprenorphine administered IV to experienced opioid users, buprenorphine was administered to 6 nondependent opioid abusers residing on a research unit; the doses tested, in separate sessions, were 12 mg buprenorphine sublingual, IV/sublingual placebo, and escalating IV buprenorphine (2, 4, 8, 12, and 16 mg). Physiologic and subjective measures were collected for 72 hours post–drug administration. Buprenorphine minimally but significantly increased systolic blood pressure. Changes in heart rate or oxygen saturation among the 7 drug conditions were not statistically significant. The mean maximum decrease in oxygen saturation from baseline was greatest for the 8-mg IV dose. Buprenorphine produced positive mood effects, although with substantial variability among participants. Onset and peak effects occurred earlier following IV administration: peak IV effects occurred between 0.25 and 3 hours; peak sublingual effects occurred at 3 to 7 hours. Duration of effects varied among the outcome measures. The dose-response curves were flat for most parameters, particularly subjective measures. Side effects were mild except in one participant who experienced severe nausea and vomiting after the 12-mg IV dose. Buprenorphine appears to have a ceiling for cardiorespiratory and subjective effects and a high safety margin even when taken by the IV route.

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Buprenorphine is a partial mu-opioid agonist used for the treatment of opioid dependence. Buprenorphine maintenance blocks the effects of opiate agonists like heroin[1] and is as effective as methadone in retaining patients in treatment and decreasing heroin use.[2–5] Since 1996, general practitioners in France have been authorized to prescribe sublingual buprenorphine for the treatment of heroin abuse; approximately 70,000 patients were receiving such prescriptions as of 2001. From 1995 to 1998, French national statistics showed decreases in the amount of heroin seized (−40%), the number of heroin-related arrests (−57%), and the number of heroin-related deaths (−76%).[6] However, this remarkable decrease in preventable drug-related deaths (from over 500 in 1994 to less than 100 in 1998) was shadowed by case reports of deaths and nonlethal intoxications associated with buprenorphine.[7–9] These cases have raised concerns about the risks of expanded use of buprenorphine. According to the statistics of the French Ministry of Interior, there were 68 prescription-medication overdoses resulting in death in 1995 (before buprenorphine) and 41 such cases in 1998 (including 13 associated with buprenorphine). Thus, the risk associated with buprenorphine appears numerically small, compared to the number of averted heroin-related deaths. In addition, almost all cases of buprenorphine overdose were associated with the coingestion of other substances, mainly benzodiazepines. (Benzodiazepines have a generally favorable safety profile when administered alone but can have adverse interactions with other drugs, especially respiratory depressants).[10–12] Therefore, it is important to characterize the risks specifically associated with buprenorphine, including intravenous (IV) self-administration.

The pharmacodynamic effects of buprenorphine are very similar to those of mu-opioid agonists such as heroin. In particular, its subjective effects are virtually identical to those of morphine and methadone.[13,14] Unlike full agonists, however, buprenorphine has been shown in animal studies to have a ceiling on its respiratory-depressant effects.[15–17] This desirable property was one of the bases for the extensive evaluation of buprenorphine for the treatment of opioid dependence. Earlier analgesia studies in humans had failed to confirm a sparing effect on respiratory functions in the perioperative period (ie, in combination with other anesthetic agents) and in patients with no documented tolerance to opioids.[18–23] However, in the same setting, a dosing

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error provided anecdotal support for buprenorphine's low toxicity,[24] and its antagonist properties were used to reverse the respiratory depression induced by fentanyl.[25]

Buprenorphine-induced respiratory depression is likely to be less prominent in dependent opiate users (the clinical population for whom buprenorphine maintenance would be most appropriate) because regular self-administration of heroin induces some degree of tolerance to respiratory depression. Such tolerance is observed to an intermediate degree in nondependent or "recreational" opioid users. Under controlled, laboratory conditions, sublingual doses of buprenorphine up to 32 mg produced minimal respiratory depression in nondependent opioid users and a ceiling for subjective effects at doses between 8 and 12 mg.[14,26] The safety and efficacy of directly observed therapy with high doses of sublingual buprenorphine have been established in the primary care setting.[5] In France, patients are routinely given 7-day supplies of 8-mg sublingual (SL) tablets to take at home.

Unfortunately, SL preparations of buprenorphine have the potential for diversion for intravenous use; they are readily soluble in water and are of adequate strength to produce significant heroin-like effects. Abuse of buprenorphine, including IV abuse, has been reported in several countries.[7,27–30] The safety of high IV doses of buprenorphine has not been systematically evaluated. It is crucial to determine whether the ceiling effects shown in humans with sublingual administration[26] are also observed after rapid intravenous administration. The present study was designed to (1) test the safety of intravenous administration of buprenorphine in the dose range used for maintenance and (2) determine whether a ceiling occurs on the effects of intravenously administered buprenorphine in experienced nondependent opioid abusers.

MATERIALS AND METHODS

Participants

The participants were 6 adult, male, nontreatment-seeking, experienced opioid users (5 African American and 1 Caucasian) who gave written informed consent and who were paid for their participation. Participants ranged in age from 32 to 40 years (mean 35.5 years) and weighed between 62.1 and 80.3 kg (mean 73.6 kg). Women and HIV-infected applicants were not excluded; however, none participated. Although not physically dependent, all were regular users of intravenous heroin and cocaine at the time they entered the study. Mean duration of heroin use was 11 ± 3 years, with a mean amount spent on heroin of US$180 ± 45 over 13 days in the last month. Mean duration of cocaine use was 13 years, with a mean amount spent on cocaine of US$660 ± 80 over 18 days in the last month. All participants were cigarette smokers, although 3 smoked less than 1 pack per day; 1 participant had a past history of alcohol abuse, and 1 of alcohol dependence. Four of six participants were current marijuana users. No participant showed any evidence of opioid or alcohol withdrawal signs while on the research unit. On the basis of physical examination, history, routine laboratory chemistries, TB tests, and psychologic screens, participants were found to be in good health and without significant psychiatric disturbance other than their drug abuse. Four additional participants enrolled: one did not complete the study due to medical reasons (weight gain associated with increased blood pressure); his data are excluded from this report. Three individuals never started the study, two due to persistent borderline high blood pressure and one due to insufficient venous access. This study was approved by the National Institute on Drug Abuse Intramural Research Program (NIDA IRP) institutional review board.

Participants lived on the inpatient research ward of the NIDA IRP during the 5- to 6-week study. Urine specimens were obtained 2 to 3 times a week and tested randomly for the presence of illicit drugs to ensure that participants were not ingesting drugs other than those administered during the study. Participants were allowed to smoke cigarettes except 120 minutes before and during the experimental sessions. Caffeine was available without restriction on the unit.

Drugs

Buprenorphine hydrochloride was obtained from Reckitt and Colman Products, Ltd., Hull, UK, (now Reckitt Benckiser Pharmaceuticals) through the National Institute on Drug Abuse, Medication Development Division. Doses were calculated based on the hydrochloride salt. Participants received a sublingual and an intravenous administration in constant volumes in each session. The sublingual solution (12 mg/mL) was prepared by the NIDA IRP pharmacy by diluting 120 mg of buprenorphine in 4.2 mL of ethyl alcohol USP 95%, adjusted to 10 mL with deionized water. The intravenous solution (4 mg/mL) was prepared in sterile water for injection by the University of Kentucky, Center for Pharmaceutical Science and Toxicology. The IV buprenorphine doses were drawn on-site and diluted in sterile water to 4 mL in the IRP pharmacy.

Buprenorphine 0-mg (SL/IV solutions), 12-mg (SL solution), and 2-, 4-, 8-, 12-, and 16-mg IV solutions were tested in 7 experimental sessions. The sublingual solution (1 mL) was administered under the tongue at the beginning of the session (buprenorphine 12 mg/mL or placebo at random for the first 2 sessions; placebo solution was administered in sessions 3 to 7). Five minutes later, a 4-mL solution with increasing buprenorphine doses (0, 0, 2, 4, 8, 12, 16 mg, respectively, in the 7 sessions) was administered intravenously over 1 minute by one of the investigators (AU) who was aware of the buprenorphine dose schedule. The participant and nursing and technical staff monitoring the session

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and collecting data were blind to the placement of the placebo doses and to the range of buprenorphine doses.

General Methods

There were 7 experimental sessions separated from one another by at least 3 days. On the morning (approximately 8:00 AM) of each session, after a light breakfast, the participant was escorted to a laboratory and seated in a cushioned reclining chair in front of a computer. Electrodes for electrocardiogram and respiration monitoring, skin temperature and oxymeter probes, and a blood pressure cuff were placed. The physician remained in the room for at least 30 minutes after drug injection or until stabilization of vital signs. One nurse and one technician were present in the room during the session to monitor the participant, draw blood, and collect data. After the end of the session, the participant returned to the residential unit; monitoring continued every 2 to 3 hours for 24 hours, then 3 times a day for 72 hours. Participants were encouraged to eat lightly and drink fluids during the day of each study session because of the known propensity of buprenorphine to cause nausea.

A desktop computer presented all questionnaires in a prearranged and timed sequence and printed and stored the data. The participants indicated their responses on a keyboard or joystick. An automated, soft auditory prompt sounded when the participant had to complete the computer tasks. Each of the measures was taken at baseline, before drug administration, and at 3- to 30-minute intervals for 3 hours after drug administration in the session room and at 2- to 12-hour intervals for 72 hours on the residential unit. Blood samples were drawn for pharmacokinetic analysis of buprenorphine (not reported here).

Physiologic Measures

Respiration rate, heart rate, blood pressure, skin temperature, and oxygen (O_2) saturation were monitored (Datascope Corporation, Paramus, NJ). To document opioid effect on miosis, the pupil diameter was measured from an image of the eye obtained by an infrared camera located in goggles (keeping the eye in dark environment) and transmitted to a video monitoring system (Sony Recorder/Monitor GV S50 NTSC Video 8 with I/R Video Goggle Assembly Serial Number 2030; equipment assembled by Eye Dynamics, Inc., Torrance, CA).

Participant-Rated Measures

Three questionnaires were completed: (1) visual analog scales, (2) an adjective rating scale of agonist/antagonist opiate effects, and (3) a shortened form of the Addiction Research Center Inventory. These measures have been described elsewhere.[31–33]

Data Analysis

Change from baseline values and area under the curve (AUC) with weighted means were calculated for the first 3 hours after drug administration (measures collected during the experimental session) and for all time points for each measure (either 55 or 72 hours). These were treated as the dependent variables in analyses of variance with one within-subjects factor (drug condition, with 7 levels). Conservative F tests employing Huynh-Feldt probability levels were used to interpret the results. Effects were considered statistically significant if $P \leq 0.05$. Analyses of variance were conducted using SPSS statistical software (SPSS Inc., Chicago, IL). For some of the physiologic effects, we also present descriptive data on time course and on maximum changes from baseline.

RESULTS

Five of six participants completed 7 study sessions of this dose-ranging buprenorphine intravenous administration study. One participant experienced severe nausea and vomiting 30 minutes after drug administration of session 6 (12 mg IV buprenorphine), and his participation was terminated. Therefore, data were analyzed with 5 participants for all 7 drug conditions and separately with 6 participants who completed 6 sessions. Statistical results reported are for the 5-participant analyses, except where specifically noted.

Time Course

The time courses of effects of buprenorphine 0 mg, 12 mg SL, and 12 mg IV are shown in Figure 1 for pupil diameter, O_2 saturation, and "Drug Effect" visual analog scale, first 3 hours (collected in the session room; left panel) and 5 to 72 hours after drug administration (right panel). The onset of effects and peak response occurred earlier following IV administration (6 to 10 minutes) compared to SL administration (20 to 90 minutes, median 60 minutes). Duration of effects varied widely across measures, as illustrated in Figure 1. Pupil constriction was long-lasting, with effects of IV buprenorphine evident at 48 hours and effects of SL buprenorphine still present at 72 hours. In contrast, no decrease in O_2 saturation was seen after the 3-hour test session. Subjective effects were intermediate in duration, lasting from 12 to 24 hours.

Physiologic Effects

Buprenorphine had generally modest effects on physiologic measures with few statistically significant differences from placebo; 3-hour AUC values for physiologic effects are shown in Figure 2. Overall, following administration of saline, blood pressure and heart rate tended to decrease during the 3-hour sessions. Significant effects of drug condition

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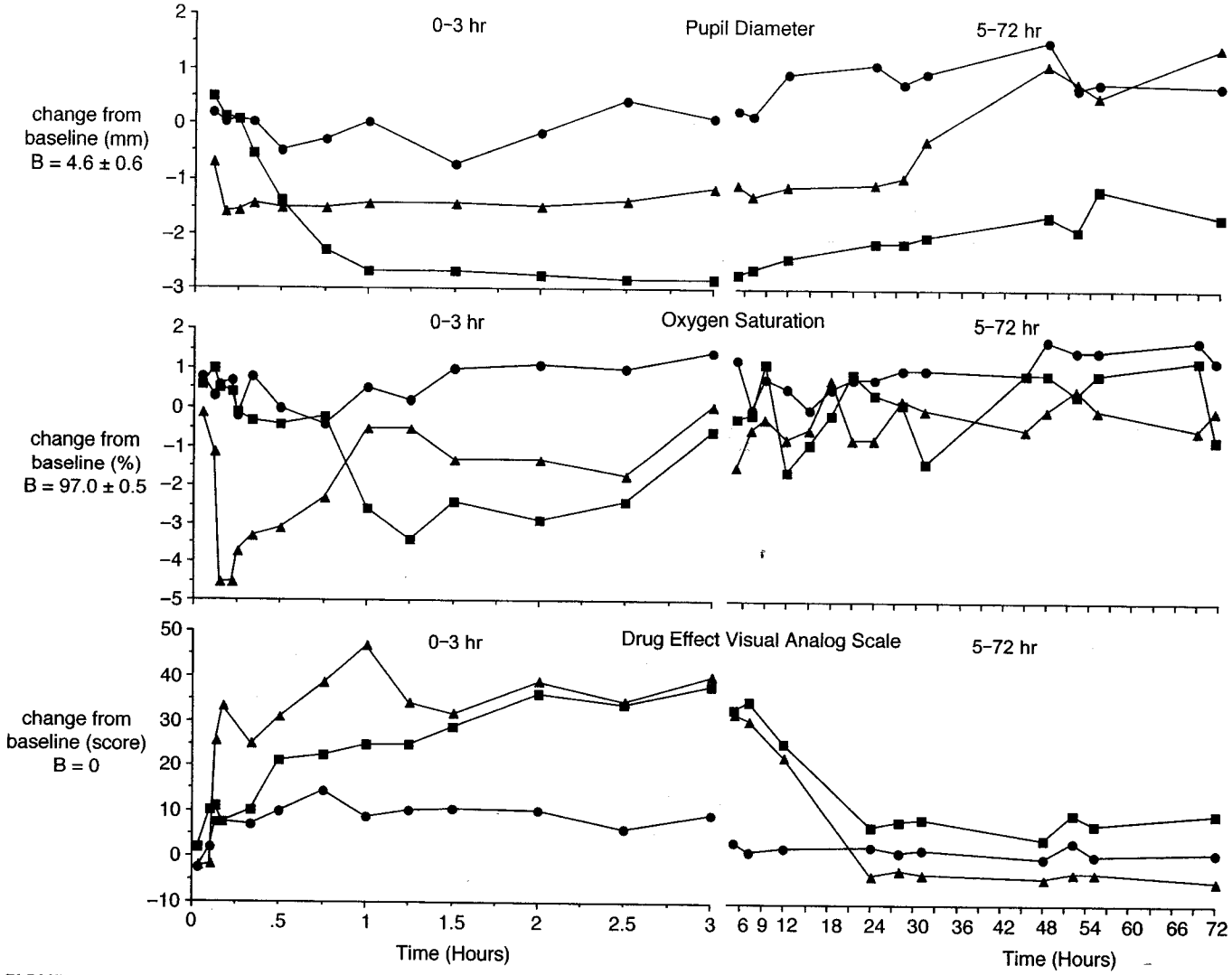

FIGURE 1. Time course of the effects of SL/IV placebo (circles), buprenorphine 12 mg SL (squares), and buprenorphine 12 mg IV (triangles) on pupil diameter, oxygen saturation, and the Drug Effect visual analog scale. Each data point represents the mean change from baseline value based on 1 observation in each of 5 participants. Standard error bars have been omitted for clarity. The left area shows results for 0 to 3 hours after drug administration, collected in the test room; the right area shows results for the data collection time 5 to 72 hours.

were seen on systolic blood pressure for the 3-hour AUC [F(6,24) = 3.22; P = 0.018], but not the 72-hour AUC [F(6,24) = 0.86; P = 0.54], with a maximum increase in systolic blood pressure observed for the 8-mg IV dose. Diastolic blood pressure and calculated mean arterial pressure also tended to increase following buprenorphine administration, most evident for 8-mg IV dose. Heart rate decreased across the 7 test conditions with no significant effect of placebo or buprenorphine dose on the 3-hour AUC values. The shape of the dose-response curve on heart rate 72-hour AUC values was similar (not shown); however, the effect of drug condition was significant [F(6,24) = 2.63; P = 0.042]. Buprenorphine effects on skin temperature were modest, with only 12 mg SL tending to increase temperature. Significant effects of drug condition were seen on pupil diameter for the 3-hour AUC [F(6,24) = 3.66; P = 0.016] and the 72-hour AUC [F(6,24) = 4.6; P = 0.003]. All doses of buprenorphine decreased pupil diameter to a similar degree in the first 3 hours, although, as indicated above, the effects of 12 mg SL were longer lasting.

Of greatest safety concern is the effect of high doses of buprenorphine on respiration. Mean 3-hour change from baseline AUC for O_2 saturation was decreased by all doses of buprenorphine to a similar degree compared to placebo, but there was no significant effect of drug condition in either 3-hour or 72-hour AUC analyses. Because means can mask

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extreme values and thus be misleading in regard to the safety of the individual, we also qualitatively examined individual maximum decreases in O_2 saturation and respiration rate for all 6 participants (Fig. 3). The mean maximum decrease in O_2 saturation from baseline appeared greatest for the 8-mg IV dose. Although effects were similar across buprenorphine doses, there was substantial individual variability. For O_2 saturation, 2 points stand out: 12 mg SL for participant 3 (maximum decrease from 98% to 85%) and 8 mg IV for participant 5 (maximum decrease from 99% to 80%). In all participants, including these 2, decreases of O_2 saturation were of a few seconds' duration and resolved spontaneously upon mild auditory stimulation of the participant. There was no apparent change in respiration rate across buprenorphine doses compared to saline. Although some participants were very drowsy at times, no participant lost consciousness during the sessions. Participant 6, who had severe nausea and vomiting following 12 mg IV and was excluded from the 16-mg IV dose, did not show a particularly strong response on O_2 saturation, although his maximum decrease was below the mean for all IV doses. Mean maximum decrease in breaths per minute was also similar across placebo and all buprenorphine doses. Breaths per minute (measured through electrocardiogram electrodes) decreased by 10 or more in 4 sessions (buprenorphine 2, 4, 8, and 16 mg IV), once in each of 4 different participants. On no occasion were these respiratory decreases associated with clinically significant decreases in O_2 saturation.

Participant-Rated Measures

The 3-hour changes from baseline AUC scores for selected participant-rated measures are shown in Figure 4. There was a significant effect of drug condition on the ratings of Drug Effect, with higher ratings following buprenorphine administration in analyses both including [$F(6,24) = 3.37$; $P = 0.015$] and excluding [$F(5,25) = 4.19$; $P = 0.007$] the 16-mg IV dose. Responses to participant-rated measures tended to have substantial variability among participants; therefore, few measures showed statistically significant dose-related effects. Buprenorphine tended to increase ratings on the Liking, Good Effects, and High (not shown) visual analog scales, although these effects were not

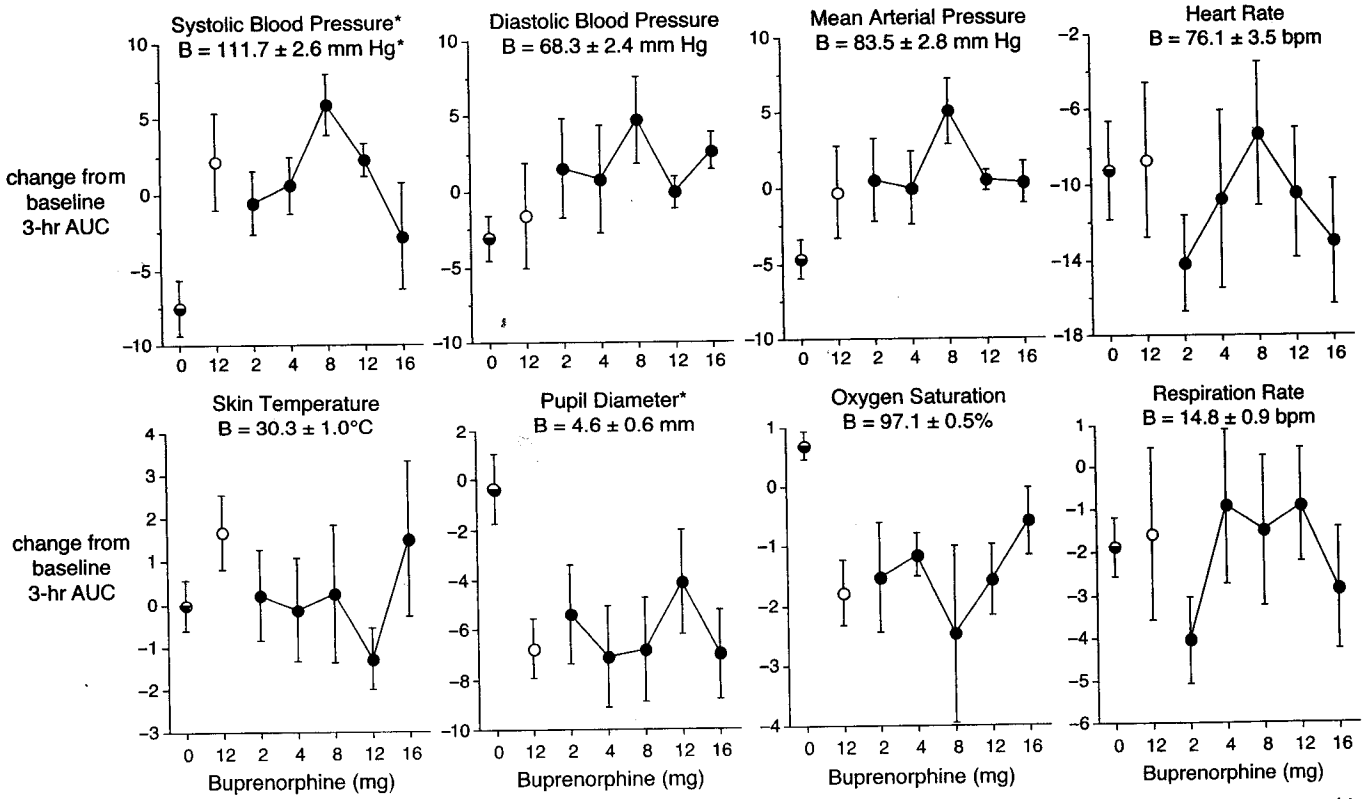

FIGURE 2. Effects of placebo and buprenorphine on systolic and diastolic blood pressure, mean arterial pressure, heart rate, skin temperature, pupil diameter, oxygen saturation, and respiration rate. Each data point represents the weighted mean change from baseline 3-hour AUC value in each of 6 participants (5 for 16 mg IV). Half-filled circles indicate SL/IV placebo; open circles indicate SL buprenorphine; and filled circles indicate IV buprenorphine. Brackets indicate SEM; asterisks indicate measures in which there was a significant effect of drug condition.

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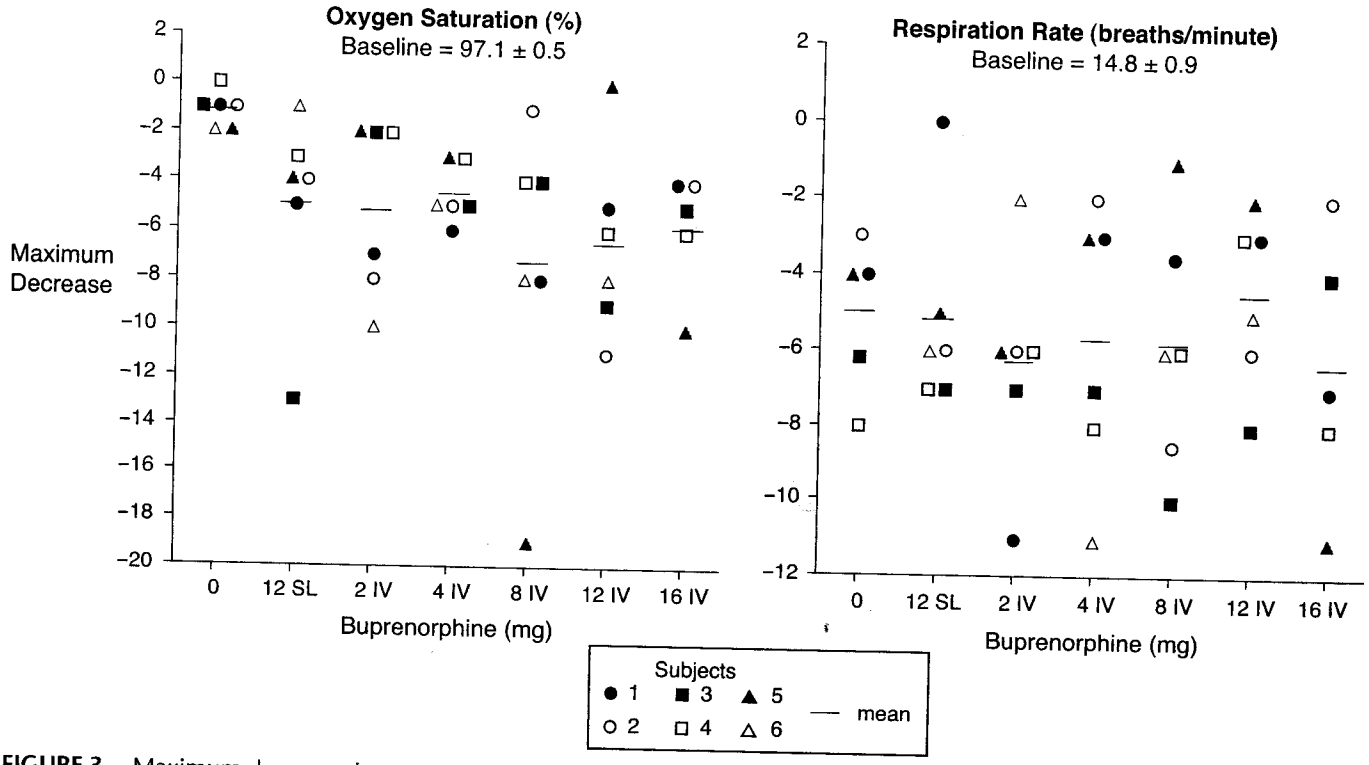

FIGURE 3. Maximum decreases in percentage oxygen saturation and respiration rate for individual participants and group mean in the first 3 hours after administration of saline and SL and IV buprenorphine. Each data point represents the maximum change from baseline for 1 participant; horizontal lines indicate the mean for the group. Data for all 6 participants are shown. No data are shown for participant 6 for buprenorphine 16 mg and for respiration rate buprenorphine 0 mg (due to missing data).

statistically significant. Few or no increases were produced on the Feel Sick, Desire for an Opiate, and Bad Effects (not shown) scales. Buprenorphine at all doses tended to increase the Agonist scale of the adjective rating scale; buprenorphine 12 mg SL also tended to increase the Antagonist scale. Analyses of the PCAG scale scores in 5 participants tested with all buprenorphine doses showed significant [$F(6,24) = 2.71$; $P = 0.037$] effect of drug condition in the 55-hour AUC scores; analyses of the PCAG scale in 6 participants excluding the buprenorphine 16-mg IV dose showed near significant [$F(5,25) = 2.86$; $P = 0.076$] and [$F(5,25) = 2.54$; $P = 0.064$] effect of drug condition in the 55-hour AUC and 3-hour AUC scores, respectively. There were no significant effects of drug condition on the MBG scale or other Addiction Research Center Inventory scales (not shown).

Clinical Observations

The main side effects observed were sedation, nausea, and itching. Participants remained responsive to low voice and computer prompts for task performance. Some participants showed irritability after study sessions, but no other changes in mental status were observed. Nearly all participants reported nausea and/or vomiting, although all but one referred to it as "the pleasant sickness" (participant 6, who was discontinued after receiving buprenorphine 12 mg IV, strongly disliked the feeling). Although the differences were not observable in self-reported measures, 4 out of the 5 patients who received the 7 doses of buprenorphine described the 16-mg IV dose as "cut" or "weaker heroin" compared to the previous dose(s).

As noted above, side effects became problematic in 1 participant during the session in which he received 12 mg IV buprenorphine. Thirty minutes after the injection, he complained of nausea and feeling cold; his vital signs were normal. He became diaphoretic and agitated due to discomfort, developed a fine tremor, and continued to report marked nausea. The participant was able to complete measurements for the session but remained nauseous and unable to eat solid food for 36 hours. He was discharged from the study fully recovered. Intermittent decreases in O_2 saturation were also observed; they did not last more than 2 to 3 seconds and always resolved spontaneously.

DISCUSSION

This study examined the effects of IV buprenorphine across a wide range of doses in participants who were experienced, nondependent opioid users. The range of doses tested included doses available in sublingual tablets for

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treatment of opioid dependence and that might be diverted for use by the IV route. The results support two major conclusions: (1) a ceiling effect of buprenorphine occurs with IV administration and (2) intravenous administration of buprenorphine in doses from 12 to 16 mg is safe in experienced, nondependent opioid abusers. The study also provides evidence for a ceiling on measures that indicate potential for abuse in that population.

Notable in the present study was the lack of dose-related effects on nearly every measure collected, indicating a ceiling on the effects of buprenorphine administered by the IV route. The overall magnitude of effects of these IV doses was similar to those of a 12 mg SL buprenorphine comparison dose but of shorter duration. In a dose-escalation study of lower IV doses (0, 0.3, 0.6, and 1.2 mg), buprenorphine's physiologic and subjective effects tended to increase with dose but were not consistently dose-related.[34] A ceiling effect has been clearly demonstrated for buprenorphine up to 32 mg administered by the SL route that was not due to limited SL absorption.[26] Thus, it appears that across a wide range of doses and with both SL and IV administration, a plateau on buprenorphine effects occurs at relatively low doses. This finding is consistent with preclinical studies showing ceilings on a range of effects[15,16,35] and with buprenorphine's classification as a partial agonist at the mu-opioid receptor.

The ceiling effect of buprenorphine was also observed for cardiorespiratory parameters, which confirmed its favorable safety profile even at high IV doses. The 16-mg IV dose represents 53 times the recommended therapeutic analgesic dose of 0.3 mg (equivalent to at least 530 mg morphine). There was no respiratory depression or other physiologic effects that were clinically significant except for severe vomiting in 1 participant. Nausea and vomiting as well as sedation were seen in most patients, but in most cases, these effects were time-limited and resolved spontaneously. The nausea seemed to be dose-dependent and should actually limit the abuse liability of buprenorphine by the IV route.

The present study included a number of subjective effect measures that have been used to predict abuse potential, such as a VAS scale of "liking" and the MBG scale of the Addiction Research Center Inventory.[36,37] Buprenorphine has been shown to produce increases in both liking and MBG scale scores in previous studies testing lower doses.[13,14,38] Within the dose range tested in the present study, buprenorphine did not significantly increase

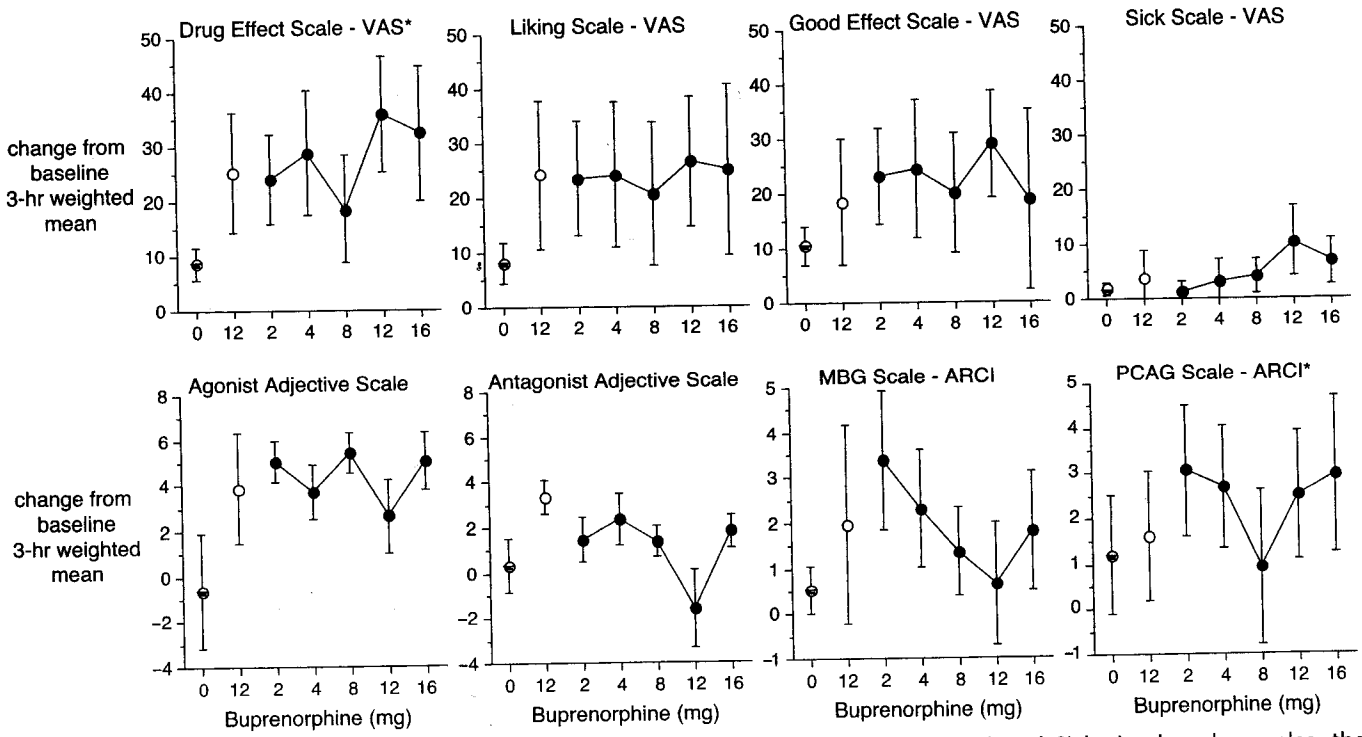

FIGURE 4. Effects of saline and buprenorphine on Drug Effect, Liking, Good Effects, and Feel Sick visual analog scales, the Agonist and Antagonist adjective rating scales, and the MBG and PCAG scales of the Addiction Research Center Inventory. Each data point represents the mean change from baseline 3-hour AUC value in each of 6 participants (5 for 16 mg IV). Half-filled circles indicate SL/IV placebo; open circles indicate SL buprenorphine; and filled circles indicate IV buprenorphine. Brackets indicate SEM; asterisks indicate measures in which there was a significant effect of drug condition.

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ratings on these scales, and its effects were not clearly dose-related, although the general direction of ratings was an increase compared to placebo (Fig. 4). Responses were extremely variable both across participants and across sessions within some participants. Buprenorphine did not uniformly produce positive mood effects (as measured by the participants' self-reports) and may have even produced unpleasant effects that counterbalanced or eliminated its positive effects.

The study has a number of limitations that reduce its generalizability. First, participants were healthy, experienced opioid users, so the results may not apply to opioid-naive individuals or those with medical conditions that might compromise respiratory or cardiovascular function (such conditions would have excluded participation in our study). Second, our sample size was relatively small and thus may not have provided power to detect subtle changes. However, a similar sample size was sufficient to detect L-alpha-acetyl-methadol (LAAM)-enhanced toxicity by the IV route.[39] Idiosyncratic vulnerabilities to the cardiovascular effects of buprenorphine may nevertheless exist, as a 22-year-old man with normal coronary arteries by angiography was reported to have experienced a myocardial infarction after using buprenorphine by inhalation.[40] Third, buprenorphine was given in a controlled environment in which participants were kept busy with study tasks; prompts from the computer regularly reminded participants to attend to the tasks, and nursing and technical staff roused participants when they appeared to doze. Greater respiratory depression might have occurred if participants had been left alone or allowed to fall asleep. Fourth, the study does not provide any information on the effects of IV buprenorphine when it is combined with other CNS depressants. Clearly, such a combination carries significant risk and is not an unlikely occurrence. Sedative use is relatively common among methadone maintenance patients,[41–44] and as mentioned earlier, a number of deaths in France have been attributed to combined use of buprenorphine and benzodiazepines.[7–9]

On the other hand, the design of the present study (with doses given in ascending order 72 to 96 hours apart) may have permitted some accumulation of buprenorphine across sessions at the higher doses. Buprenorphine is known to have a long half-life and to be detectable past 72 hours following a single 32-mg SL dose.[26,45] Such accumulation of buprenorphine would be expected to have enhanced its depressant effects.

In summary, buprenorphine administered intravenously in doses ranging from 2 to 16 mg produced substantial subjective and physiologic effects. A ceiling effect was clearly apparent on a range of measures across the dose range tested. Nausea and vomiting were the most common adverse effects and were clinically significant in severity and duration, and these may decrease the abuse potential by the IV route. Sedation was also common, but participants were easily roused. Respiratory depression occurred but was relatively brief and not medically significant. Finally, although participants reported subjective effects consistent with abuse potential, their responses were quite variable and not consistently pleasurable.

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The Editors

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