Effects of Infusion Rate of Intravenously Administered Morphine on Physiological, Psychomotor, and Self-Reported Measures in Humans

LISA A. MARSCH, WARREN K. BICKEL, GARY J. BADGER, JAMES P. RATHMELL, MICHAEL D. B. SWEDBERG, BROR JONZON, and CARINA NORSTEN-HÖÖG

Department of Psychiatry (L.A.M., W.K.B.), Department of Medical Biostatistics (G.J.B.), and Department of Anesthesiology (J.P.R.), University of Vermont, Burlington, Vermont; and AstraZeneca R&D Södertälje, Södertälje, Sweden (M.D.B.S., B.J., C.N.-H.)

Received May 9, 2001; accepted August 21, 2001

ABSTRACT

Although the rate of onset of a drug effect is commonly believed to contribute to a drug’s abuse liability, only a few systematic experimental studies have been conducted examining this notion. The present study determined the profile of physiological, psychomotor, and self-reported effects of infusion rate (a key means of manipulating onset of drug action) of intravenously administered morphine, the prototypical analgesic with a known abuse liability in human participants. Two doses of morphine sulfate (5 and 10 mg/70 kg, i.v.) and a placebo dose (0 mg/70 kg, i.v.) were administered to healthy volunteers under three infusion rates (2 min bolus, 15 min, and 60 min). Faster infusions of morphine produced greater positive subjective effects than slower infusions on visual analog scale measures of good drug effect, drug liking, and high. Faster infusions also resulted in greater self-reported drug effects and opioid agonist effects, without producing significant physiological or psychomotor impairment. Importantly, faster rates of drug infusion produced significantly higher morphine plasma levels than slower rates, and morphine plasma levels followed a similar pattern and timing of peak effect as the self-reported effects of the drug. Moreover, morphine produced dose-dependent increases in self-reported drug effects, opioid agonist effects, and morphine plasma levels in the study. Results suggest that the pharmacokinetic properties of a drug, including the dosage administered and the rate of at which it is administered may function to jointly affect the abuse liability of the drug.

The abuse liability of a drug is dependent on various pharmacokinetic properties, including its route of administration, the dosage administered, and the rate of onset of its effects (Farre and Cami, 1991). Although it has been repeatedly and empirically demonstrated that the euphorogenic subjective effects and enhanced self-administration of a drug depend upon a drug’s route of administration and dose, only limited systematic experimental data support the commonly held belief that the rate of onset of drug effects contributes to a drug’s reinforcement value (deWit et al., 1992; Mumford et al., 1994).

Manipulating infusion rate of a drug is a key means of examining the effects of onset of drug effects. Although the rate of onset of drug effects, in general, and the rate of a drug infusion, in particular, are commonly believed to contribute to a drug’s abuse liability, such that a faster onset of a drug produces greater drug liking than a slower onset, only a few systematic experimental studies have been conducted examining this notion (deWit et al., 1992; Mumford et al., 1994). Additionally, only a limited amount of experimental research has examined whether a faster onset of drug produces greater drug liking by producing higher blood levels (e.g., a higher effective unit dose of the drug).

A few laboratory studies have investigated the role of the rate of onset of drug effects with orally administered drugs in humans. For example, one study found that when a single dose (fast onset) and six divided doses (slow onset) of pentobarbital produced similar peak plasma levels in humans, participants who received the fast drug onset reported greater subjective “liking” of the drug and reached greater peaks in their ratings of “high” (deWit et al., 1992). In addition, extended-release orally administered alprazolam has been demonstrated to have less abuse potential relative to immediate-release alprazolam in individuals with a history of sedative abuse (Mumford et al., 1994).

ABBREVIATIONS: ARS, adjective rating scale; VAS, visual analog scale; ARCI, Addiction Research Center Inventory; DSST, Digit Symbol Substitution Test; M6G, morphine-6-glucuronide; M3G, morphine-3-glucuronide; PCAG, pentobarbital-chlorpromazine-alcohol group; MBG, morphine-benzedrine group; LSD, lysergic acid diethylamide; BG, benzodrine group; A, amphetamine.
Materials and Methods

Subjects

Eighteen healthy male subjects, 18 to 45 years of age, participated in this study. Mean age of subjects was 25.4 (range 19–38). Participants were recruited from newspaper and bulletin board advertisements. This sample size was determined based on data from a previous study corresponding to dose effect curves for “peak effect” and “area under the curve” in morphine with the same outcome measures that were used in the present study (Petry et al., 1998).

During their initial visit, subjects received a full medical evaluation, including a medical, psychiatric, and drug abuse history, physical exam, laboratory work, and EKG. Laboratory work included tests of various liver enzymes (alanine aminotransferase, aspartate aminotransferase), creatinine, thyroid stimulating hormone, and a complete blood count. Individuals with any significant medical (e.g., liver or thyroid disorder) or psychiatric disorder, a past or current history of renal failure, or a past or current history of alcohol or other drug (non-nicotine) dependence were excluded from study participation. Subjects either had prior experience with opioids in a medical setting (i.e., 2–20 prior uses) or were opioid-naïve. Individuals who reported that they had recreationally used opioids were not allowed to participate.

This study was approved by the Institutional Review Board for human research at the University of Vermont (Burlington, VT). All subjects provided written informed consent prior to participation in the research study after receiving a full explanation of the procedures. All subjects were paid for their participation.

Experimental Procedures

General Procedures. After the initial visit, each of nine experimental sessions were conducted on an outpatient basis at the Fletcher Allen Health Care Clinical Research Center (Burlington, VT) and lasted approximately 4 h. All 18 subjects received all nine experimental conditions (three doses × three infusion rates) in a randomly assigned order. Study sessions were separated by a minimum of 3 days. That is, each subject attended two sessions per week for approximately 4.5 weeks (Monday/Thursday or Tuesday/Friday sessions). Subjects were instructed to abstain from alcohol for 24 h and caffeine, nicotine, solid food, and liquids other than alcohol (including water) for 4 h prior to study sessions. Moreover, subjects were instructed to abstain from all illicit drugs (i.e., opioids, stimulants, cannabinooids, barbiturates, or benzodiazepines) during the study.

On arrival at the laboratory, subjects were required to pass a Breathalyzer test (for alcohol) and a field sobriety test and to provide a urine sample. Breathalyzer recordings were required to be equal to zero for a subject to participate in a study session. Urine samples collected at each session were screened for illicit drugs on a random basis using our enzyme-mediated immunoassay technique urinanalysis system (Syva, Palo Alto, CA) to ensure compliance with the study instructions.

Sessions were conducted in a quiet temperature-controlled laboratory. Subjects were required to remain semisupine for the duration of the study session. Initially, subjects completed a battery of dependent measures (described below). Following completion of the test battery, either drug or placebo was administered intravenously using standard aseptic procedures (described below). Dependent measures were collected at periodic intervals for the following 3 h. Subjects were allowed to engage in sedentary activities, such as reading, during the testing session when assessments were not scheduled. Subjects were allowed to drink water during the sessions but were not allowed to eat until the study session was completed. Before being discharged, all subjects were required to pass a field sobriety

Materials and Methods

Subjects

Eighteen healthy male subjects, 18 to 45 years of age, participated in this study. Mean age of subjects was 25.4 (range 19–38). Participants were recruited from newspaper and bulletin board advertisements. This sample size was determined based on data from a previous study corresponding to dose effect curves for “peak effect” and “area under the curve” in morphine with the same outcome measures that were used in the present study (Petry et al., 1998).

During their initial visit, subjects received a full medical evaluation, including a medical, psychiatric, and drug abuse history, physical exam, laboratory work, and EKG. Laboratory work included tests of various liver enzymes (alanine aminotransferase, aspartate aminotransferase), creatinine, thyroid stimulating hormone, and a complete blood count. Individuals with any significant medical (e.g., liver or thyroid disorder) or psychiatric disorder, a past or current history of renal failure, or a past or current history of alcohol or other drug (non-nicotine) dependence were excluded from study participation. Subjects either had prior experience with opioids in a medical setting (i.e., 2–20 prior uses) or were opioid-naïve. Individuals who reported that they had recreationally used opioids were not allowed to participate.

This study was approved by the Institutional Review Board for human research at the University of Vermont (Burlington, VT). All subjects provided written informed consent prior to participation in the research study after receiving a full explanation of the procedures. All subjects were paid for their participation.

Experimental Procedures

General Procedures. After the initial visit, each of nine experimental sessions were conducted on an outpatient basis at the Fletcher Allen Health Care Clinical Research Center (Burlington, VT) and lasted approximately 4 h. All 18 subjects received all nine experimental conditions (three doses × three infusion rates) in a randomly assigned order. Study sessions were separated by a minimum of 3 days. That is, each subject attended two sessions per week for approximately 4.5 weeks (Monday/Thursday or Tuesday/Friday sessions). Subjects were instructed to abstain from alcohol for 24 h and caffeine, nicotine, solid food, and liquids other than alcohol (including water) for 4 h prior to study sessions. Moreover, subjects were instructed to abstain from all illicit drugs (i.e., opioids, stimulants, cannabinoids, barbiturates, or benzodiazepines) during the study.

On arrival at the laboratory, subjects were required to pass a Breathalyzer test (for alcohol) and a field sobriety test and to provide a urine sample. Breathalyzer recordings were required to be equal to zero for a subject to participate in a study session. Urine samples collected at each session were screened for illicit drugs on a random basis using our enzyme-mediated immunoassay technique urinanalysis system (Syva, Palo Alto, CA) to ensure compliance with the study instructions.

Sessions were conducted in a quiet temperature-controlled laboratory. Subjects were required to remain semisupine for the duration of the study session. Initially, subjects completed a battery of dependent measures (described below). Following completion of the test battery, either drug or placebo was administered intravenously using standard aseptic procedures (described below). Dependent measures were collected at periodic intervals for the following 3 h. Subjects were allowed to engage in sedentary activities, such as reading, during the testing session when assessments were not scheduled. Subjects were allowed to drink water during the sessions but were not allowed to eat until the study session was completed. Before being discharged, all subjects were required to pass a field sobriety
test from the laboratory and were given a light snack. In addition, subjects were required to agree not to drive a car, ride a bicycle, or operate machinery for 8 h after a session and to restrict other activities according to the advice of the study investigators.

**Drugs.** Placebo (0 mg or saline) and morphine sulfate (5 or 10 mg/70 kg, i.v.) were administered by a registered nurse at one of three infusion rates: a bolus infusion rate of 2 min, an infusion rate of 15 min, or an infusion rate of 60 min. The registered nurse, the study participants, and the research assistants overseeing data collection during study sessions were blind with respect to the treatments. These individuals were told that participants could receive drugs from one of five classes: sedatives, stimulants, analgesics, alcohol, or placebo. A nonblind investigator was available during all study sessions in the unexpected event that the blind had to be broken for a given participant, although no such event occurred in the study.

Each subject was randomly exposed to each of nine study conditions with one constraint; namely, subjects were required to be exposed to the bolus infusion of 5 mg/70 kg of morphine before being exposed to the highest bolus dose of morphine (10 mg/70 kg) for safety reasons. All patients tolerated the 5 mg/70 kg dose without incident and went on to receive the 10-mg dose. The 3-day intersession interval allowed adequate time for clearance of morphine. Morphine sulfate was obtained from commercially available product in sterile injectable form. Saline placebo was obtained from the Fletcher Allen Health Care Investigational Drug Pharmacy. To maintain blinding, we used different concentrations of vehicle and active drug in a constant volume to vary the dose. This procedure was used to control for the quantity of fluid entering the body.

Doses of active morphine that were selected for inclusion in this study are within morphine’s analgesic dose range and have been successfully and safely used with minimal adverse effects (Jaffe and Martin, 1990; Obhyst et al., 1991; Barr and Donner, 1995). For example, Foltin and Pischman (1992) administered 0, 5, and 10 mg/70 kg of morphine over 10 s to adult males with histories of intravenous cocaine and heroin use without producing any notable adverse effects. In addition, in three separate studies, Zacny and colleagues (Zacny et al., 1994b, 1997; Walker and Zacny, 1999) administered 10 mg/70 kg of i.v. morphine to healthy nondrug abusing volunteers (the same population sampled in the present study) without serious adverse effects. Moreover, in another study (Stanski et al., 1978), 10 mg of i.v. morphine was safely administered to healthy young adult males.

The decision to adjust dose based on participant weight instead of using absolute doses independent of weight was made for two primary reasons. First, this procedure was followed to ensure participant safety (e.g., to ensure that doses administered were weight appropriate and to prevent clients who weighed less from receiving a dose that they may not tolerate well). Second, this procedure ensured experimental control over the dose effects experienced by participants. That is, as persons with differing weights may experience the effects of various doses of opiates differently, this procedure ensured that the actual dose experienced by participants was held constant across participants and did not differ based on body weight. Weight tended to be similar across participants. Mean weight of participants was 75.9 kg (range was from 59.5 to 98.3 kg; S.E.M. = 2.90), and thus absolute doses administered to participants were similar.

Resuscitation equipment (including naloxone) were readily available during all sessions in case of respiratory depression, although there was never a need to use these devices during the study. Additionally, an anesthesiologist was immediately available during all study sessions.

**Blinding Infusion Rates.** Infusions were either 2, 15, or 60 min in duration in a blinded fashion. Subjects in all conditions received an hour-long infusion composed of drug and/or saline (depending on their infusion rate and dose condition). That is, three separate pumps were set up to be activated by a nurse at time 0, 45, and 58 min for subjects in the 60-, 15-, and 2-min infusion rate conditions, respectively. Thus, subjects receiving an hour-long infusion of drug received drug at all three time points. Subjects in the 15-min drug infusion condition received saline at time 0 min and drug at times 45 and 58 min. Subjects in the 2-min bolus drug infusion received saline at times 0 and 45 and drug at time 58 min.

**Dependent Measures.** Dependent measures were collected just prior to and 15, 30, 45, and 60 min after the onset of the hour-long drug and/or saline infusion, as well as 15, 30, 45, 60, 90, and 120 min after the termination of the infusion. We used these temporal parameters for collecting measurements to compare physiological, psychomotor, and self-report measures both during and after drug infusions. The specific timing parameters were also selected to correspond to the infusion rate methodology that we employed in our study design. Subjects were seated in front of a Macintosh G3 laptop screen and numeric keypad. The self-report questions and psychomotor task were presented on the monitor. Subject manipulations of the keys were recorded by the computer. It took an average participant approximately 15 min to complete the entire test battery. A research assistant was present in the session room at all times and was responsible for overseeing the collection of all dependent measures in accordance with the session time line. A summary of the time line for collecting the dependent measures and activating the saline/drug pumps is provided in Table 1.

**Self-Report Measures.** The subjective effects of the three infusion rates and three doses of morphine were compared using several self-report questionnaires: VAS, ARS, and the ARCI.

**VAS.** On this measure (Preston et al., 1988), subjects rated the extent to which they experienced six effects (drug effect, drug liking, good drug effects, bad drug effects, drug-induced high, and sick). The analog scales consisted of a line approximately 100 mm in length, anchored at each end by “not at all” and “severe”. Subjects were instructed to move a cursor along the line reflecting the degree to which they were currently experiencing each of the six drug effects. Responses were recorded as a score ranging from 0 to 100.

**ARS.** Self reports of drug effects were rated on a modified version of an adjective rating scale (Bickel et al., 1988) listing 32 items describing typical opioid drug effects and withdrawal effects. Subjects were instructed to move a cursor along a line anchored at each end by “not at all” and “severe” for each symptom they have experienced. Responses were recorded as a score ranging from 0 to 9. Opioid drug effects included nodding, rush, loaded/high, coating, itchy skin etc., and withdrawal effects included such items as irritability, chills/gooseflesh, runny nose, yawning etc.

**ARCI short form.** Subjects completed this 49-item true-false questionnaire derived from a 500-item questionnaire containing numerous empirically derived drug-sensitive scales (Haertzen, 1970; Martin et al., 1971). The five major scales of this questionnaire are PCAG (a measure of sedation), MBG (a measure of euphoria), LSD (a measure of dysphoria and psychotomimetic effects), and BG and A (amphetamine-sensitive scales).

**Psychomotor Task.** Psychomotor performance was assessed using a computerized version of the Digit Symbol Substitution Test (DSST) (McLeod et al., 1982). The digits 1 to 9 were displayed continuously at the top of the microcomputer screen, each associated with a three-step symbol (a measure of dysphoria and psychotomimetic effects), and BG and A (amphetamine-sensitive scales). The digits 1 to 9 were displayed continuously at the top of the microcomputer screen, each associated with a three-step symbol and numeric keypad. The self-report questions and psychomotor task were presented on the monitor. Subject manipulations of the keys were recorded by the computer. It took an average participant approximately 15 min to complete the entire test battery. A research assistant was present in the session room at all times and was responsible for overseeing the collection of all dependent measures in accordance with the session time line. A summary of the time line for collecting the dependent measures and activating the saline/drug pumps is provided in Table 1.
<table>
<thead>
<tr>
<th>Condition</th>
<th>Procedure</th>
<th>Time (min)</th>
<th>Battery 1</th>
<th>Battery 2</th>
<th>Battery 3</th>
<th>Battery 4</th>
<th>Battery 5</th>
<th>Battery 6</th>
<th>Battery 7</th>
<th>Battery 8</th>
<th>Battery 9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>Infusion</td>
<td>0</td>
<td></td>
<td>9</td>
<td>10</td>
<td></td>
<td>10</td>
<td>10</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>Infusion</td>
<td>15</td>
<td></td>
<td>9</td>
<td>10</td>
<td></td>
<td>10</td>
<td>10</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>Infusion</td>
<td>30</td>
<td></td>
<td>9</td>
<td>10</td>
<td></td>
<td>10</td>
<td>10</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>Infusion</td>
<td>45</td>
<td></td>
<td>9</td>
<td>10</td>
<td></td>
<td>10</td>
<td>10</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>Infusion</td>
<td>50</td>
<td></td>
<td>9</td>
<td>10</td>
<td></td>
<td>10</td>
<td>10</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>Infusion</td>
<td>58</td>
<td></td>
<td>9</td>
<td>10</td>
<td></td>
<td>10</td>
<td>10</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>Infusion</td>
<td>60</td>
<td></td>
<td>9</td>
<td>10</td>
<td></td>
<td>10</td>
<td>10</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>Infusion</td>
<td>75</td>
<td></td>
<td>9</td>
<td>10</td>
<td></td>
<td>10</td>
<td>10</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>Infusion</td>
<td>90</td>
<td></td>
<td>9</td>
<td>10</td>
<td></td>
<td>10</td>
<td>10</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>Infusion</td>
<td>105</td>
<td></td>
<td>9</td>
<td>10</td>
<td></td>
<td>10</td>
<td>10</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>Infusion</td>
<td>120</td>
<td></td>
<td>9</td>
<td>10</td>
<td></td>
<td>10</td>
<td>10</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>Infusion</td>
<td>150</td>
<td></td>
<td>9</td>
<td>10</td>
<td></td>
<td>10</td>
<td>10</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>Infusion</td>
<td>180</td>
<td></td>
<td>9</td>
<td>10</td>
<td></td>
<td>10</td>
<td>10</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Physiologic Measures**

Pupil constriction, or miosis, a physiologic indicator of μ-opioid effects, was determined before and following drug administration from photographs taken with a Polaroid close-up camera at 2× magnification at 1 footcandle of ambient illumination (Polaroid, Cambridge, MA). Pupil diameter was measured from these photographs by a research assistant who was blind to experimental conditions.

Systolic and diastolic blood pressure, heart rate, skin temperature, and arterial oxygen saturation were continuously measured and monitored by a trained research assistant throughout the session and were documented by the research assistant once every 15 min. Systolic and diastolic blood pressure (mm Hg) were determined oscillographically by a Sentron blood pressure monitor with an automatically inflating cuff (Sentron, Gig Harbor, WA). Heart rate sampled during the blood pressure measurement was converted to beats per minute by the Sentron monitor. Skin temperature was measured via a finger thermistor. Arterial oxygen saturation (O₂ saturation of the hemoglobin in a sample of blood) was monitored via a pulse oximeter (BCI 3301 Oximeter; BCI International, Waukesha, WI).

Respiration rate was assessed in accordance with the following procedure, which has been used successfully in several studies at the hospital Clinical Research Center (where the study was conducted). Specifically, a registered nurse at the Clinical Research Center collected a pre-session baseline measure of a given subject’s respiration rate by visually observing and systematically documenting the rate of the rise and fall of the subject’s chest for a 1 min duration. In a similar manner, the nurse assessed a subject’s respiration rate 15, 45, 50, 58, and 60 min after the start of the hour-long drug or saline infusion and 15, 30, and 120 min after the termination of the infusion. The registered nurse documented subjects’ respiration rate at each time of assessment.

Blood samples (5 ml each) were drawn by a registered nurse at six time points during each of the nine experimental sessions (baseline, 15, 50, 60, 90, and 180 min) (see Table 1). All blood samples were drawn from participants via an intravenous catheter inserted into their forearm that enabled blood to be drawn into a heparinized tube. Whole blood was taken in heparinized tubes during each blood draw. The plasma was separated by centrifugation at room temperature within 30 min of collection. Each plasma sample was transferred into polypropylene tubes (Nunc CryoTubes; NUNC A/S, Roskilde, Denmark) using a glass pipette and then immediately frozen and stored at −80°C until it was shipped on dry ice to AstraZeneca R&D Söder- tälje (Södertälje, Sweden) for analysis. Analyses of morphine and the metabolites morphine-6-glucuronide (M6G) and morphine-3-glucuronide (M3G) were conducted on the blood samples. In these analyses, the parent drug and its metabolites were isolated from plasma by solid phase extraction and determined by reversed-phase liquid chromatography with mass spectrometric detection. The lower limit of quantification was 1.5 nM for morphine, 10 nM for M3G and 2 nM for M6G. The analyses performed were validated by the use of quality control samples, prepared in plasma, treated the same as the unknown samples, and included in each batch undergoing analysis. The interassay accuracy and precision were determined from duplicates of quality-control samples at three different concentrations within the calibration range.

**Data Analysis**

Repeated measures analysis of variance corresponding to a 3 × 3 within-subjects design was conducted for each outcome measure individually, including subjective, physiologic, and psychomotor outcomes. Peak change from baseline was the primary outcome measure used to examine differences between treatment conditions over the post-treatment period. Analyses were also conducted based on area under the curve, but these analyses are not presented, as they closely parallel peak change results. A second set of repeated measures analyses of variance, testing for differences in infusion...
rate, were performed on the data when restricted to the two active dose conditions (3 × 2 within-subject, placebo excluded). This procedure was followed because no infusion rate effects were expected or observed under the placebo dosing condition. Exclusion of the placebo data increased the statistical power to detect effects of infusion rate under active dosing conditions, which was the primary focus of the study. Pairwise comparisons between dosing conditions and infusion rates were performed using Fisher’s least significant difference. Statistical analyses were performed using SAS statistical software (PROC GLM; SAS, Cary, NC). All tests of significance were performed at a two-sided α = 0.05. All statistical analyses were conducted at the study site.

Results

No significant interaction was detected between infusion rate and morphine dose (F test, p > 0.05 for all outcome measures). Thus, this section focuses on the main effects of each factor, with the corresponding means presented in Table 2. For descriptive purposes, the simple effects (e.g., infus-rate and morphine dose (F test, p = 0.0008), high (F (2,34) = 7.30; p = 0.0023), and good (F (2,34) = 16.20; p = 0.0001). Pairwise comparisons revealed that on the measures of drug liking and good, the bolus and 15-min infusions produced significantly greater higher scores compared with the 60-min infusion; however, the bolus and 15-min infusion rate conditions did not differ from one another. As is evident in Fig. 1, the bolus infusion rate produced slightly higher mean peak change scores relative to the 15-min infusion on the measure of drug liking under the 5 mg/70 kg dosing condition but not under the 10 mg/70 kg dosing condition. However, as previously discussed, no significant dose × infusion rate interaction was observed on this or any other outcome measure, and thus one must interpret these simple effects with caution. Furthermore, on the VAS measure of high, the bolus infusion produced significantly higher scores compared with both the 15- and 60-min infusions. Although the 15-min infusion rate produced slightly higher mean peak change scores than the 60-min infusion rate on this measure of high under the 10 mg/70 kg dosing condition but not under the 5 mg/70 kg dosing condition, the 15- and 60-min infusions

<table>
<thead>
<tr>
<th>TABLE 2</th>
<th>Mean (and S.E.M.) peak change from baseline for all subjective, psychomotor, and physiological effects for all main effects of infusion duration and dose conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outcome Measure</td>
<td>Infusion Duration*</td>
</tr>
<tr>
<td></td>
<td>60 min</td>
</tr>
<tr>
<td><strong>Visual Analog Scales</strong></td>
<td></td>
</tr>
<tr>
<td>Drug Effect</td>
<td>35.42 (4.17)b</td>
</tr>
<tr>
<td>Liking</td>
<td>27.56 (4.80)b</td>
</tr>
<tr>
<td>High</td>
<td>24.17 (5.14)b</td>
</tr>
<tr>
<td>Good</td>
<td>29.58 (4.59)b</td>
</tr>
<tr>
<td>Bad</td>
<td>15.42 (3.45)b</td>
</tr>
<tr>
<td>Sick</td>
<td>10.64 (3.53)ab</td>
</tr>
<tr>
<td><strong>Adjective Rating Scales</strong></td>
<td></td>
</tr>
<tr>
<td>Agonist</td>
<td>15.19 (2.68)ab</td>
</tr>
<tr>
<td>Antagonist</td>
<td>5.83 (1.20)a</td>
</tr>
<tr>
<td>ARC1</td>
<td>2.08 (0.50)b</td>
</tr>
<tr>
<td>LSD</td>
<td>2.64 (0.62)a</td>
</tr>
<tr>
<td>PCAG</td>
<td>0.19 (0.65)a</td>
</tr>
<tr>
<td>MBG</td>
<td>0.81 (0.04)a</td>
</tr>
<tr>
<td><strong>Physiological Measures</strong></td>
<td></td>
</tr>
<tr>
<td>Number Correct</td>
<td>-1.90 (1.44)a</td>
</tr>
<tr>
<td>Pupil Diameter</td>
<td>-0.93 (0.29)b</td>
</tr>
<tr>
<td>Respiration Rate</td>
<td>-2.19 (0.89)b</td>
</tr>
<tr>
<td>Oxygen Saturation</td>
<td>0.11 (0.37)c</td>
</tr>
<tr>
<td>Heart Rate</td>
<td>-2.31 (1.87)c</td>
</tr>
<tr>
<td>Systolic Blood Pressure</td>
<td>-3.36 (2.89)b</td>
</tr>
<tr>
<td>Diastolic Blood Pressure</td>
<td>-2.50 (2.38)c</td>
</tr>
<tr>
<td>Skin Temperature</td>
<td>-2.86 (0.81)b</td>
</tr>
<tr>
<td>Plasma Levels (in nmol/l)</td>
<td></td>
</tr>
<tr>
<td>Morphine</td>
<td>684 (75)e</td>
</tr>
<tr>
<td>M3G</td>
<td>280 (20)</td>
</tr>
<tr>
<td>M6G</td>
<td>44.9 (3.4)b</td>
</tr>
</tbody>
</table>

* Means sharing a common superscript letter are not significantly different (Fisher’s least significant difference, p < 0.05). All data refer to mean (and S.E.M.) peak change from baseline.

** Means presented correspond to active doses of morphine (5 mg/70 kg and 10 mg/70 kg).
did not significantly differ from one another, and as previously noted, no significant dose times infusion rate interaction was observed.

Significant main effects of infusion rate were also observed on the VAS measures of bad (\(F_{(2,34)} = 9.11; p = 0.0007\)) and sick (see Table 2; \(F_{(2,34)} = 5.78; p = 0.0069\)). Pairwise comparisons revealed that the bolus infusion rate produced significantly higher scores on the measure of bad than both the 15- and 60-min infusions, which did not differ from one another. Additionally, the bolus infusion produced significantly higher scores than the 60-min infusion on the VAS measure of sick; however, the 15-min infusion did not produce scores significantly different from either the bolus or 60-min infusions.

**Dose effects.** Scores on all VAS measures (including drug effect, drug liking, high, good, bad, and sick) were significantly different across dosing conditions (F test, \(p < 0.05\) for main effect of dose on all measures). Pairwise comparisons revealed that each of the three doses (placebo, 5 mg/70 kg, and 10 mg/70 kg) was significantly different from every other dose condition for VAS measures of drug effect, drug liking, high, and good. For the VAS measure of bad, the two active doses differed from placebo but did not differ from one another. On the measure of sick, only the 10 mg/70 kg dose differed from placebo.

**Adjective Rating Scale.** The fifth panel in Fig. 1 shows peak change scores for the adjective agonist measure of the ARS for each infusion rate and dosing condition.

**Infusion rate effects.** As depicted in Fig. 1, a significant effect of infusion rate was observed on the opioid agonist measure of the ARS (\(F_{(2,34)} = 6.47; p = 0.004\)), with the bolus and 15-min infusions producing higher scores on this measure compared with the 60-min infusion. No infusion rate effects were evident, however, on the opioid antagonist measure of the ARS (\(F_{(2,34)} = 0.47; p = 0.62\)).

**Dose effects.** Scores on both the agonist and antagonist measures of the ARS were significantly different across the dosing conditions (\(F_{(2,34)} = 22.2, p = 0.0001\) and \(F_{(2,34)} = 4.29, p = 0.02\), respectively). The higher dose of morphine (10 mg/7 kg) produced significantly higher scores on the agonist measure of the ARS compared with the lower dose of morphine (5 mg/70 kg), and both active doses were significantly higher than placebo; however, only the higher dose of morphine was significantly different from placebo on the antagonist measure of the ARS.

**ARCI.** The last panel in Fig. 1 shows peak changes for the LSD scale of the ARCI for each infusion rate and dosing condition.

**Infusion rate effects.** As is shown in Fig. 1, significant effects of infusion rate were observed on the LSD scale of the ARCI (\(F_{(2,34)} = 5.87; p = 0.006\), with the bolus infusion producing higher scores on this measure compared with the 15- and 60-min infusions. No other significant infusion rate effects were observed on any other ARCI scale, including the PCAG, MBG, BG, and A scales (\(p > 0.15\) for all measures).

**Dose effects.** Scores on the LSD, MBG, PCAG, and A scales of the ARCI were significantly different across dosing conditions (F test, \(p < 0.05\) in all cases). The higher dose of
morphine (10 mg/70 kg) produced significantly higher scores on the LSD scale compared with the lower dose of morphine (5 mg/70 kg), and both active doses produced scores that differed from placebo. For PCAG, both active doses differed from placebo, whereas for MBG and A only the 10 mg/70 kg dose produced higher scores than placebo. No significant dose effect was observed on the ARCI measure of Benzedrine (F(2,34) = 1.72, p = 0.19).

Psychomotor Performance

Infusion rate effect. Neither the number of items participants attempted to complete nor the number of items correctly matched by participants on the DSST measure were significantly affected by infusion rate of morphine (F(2,34) = 1.5, p = 0.23 and F(2,34) = 0.81, p = 0.45, respectively).

Dose effects. Both the number of items participants attempted to complete on the DSST measure and the number of items correctly matched by participants on this measure were significantly different across the three dosing conditions (F(2,34) = 10.9, p = 0.0002 and F(2,34) = 8.7, p = 0.0009, respectively). Both of these items were significantly lower when participants were exposed to the higher dose of morphine (10 mg/70 kg) than when exposed to the lower dose of morphine (5 mg/70 kg). In neither case was the lower dose significantly different from placebo.

Physiologic Measures

Infusion rate effect. No significant effects of infusion rate were observed on measures of pupil diameter, respiration rate, oxygen saturation, pulse, systolic blood pressure, or diastolic blood pressure (F(2,34) > 0.15 in all measures). Skin temperature was the only physiologic measure on which an infusion rate effect was observed (F(2,34) = 5.05; p = 0.012), with the bolus infusion producing significantly greater differences in skin temperature than the 15-min infusion rate. However, the 60-min infusion rate did not significantly differ from either the bolus or 15-min infusions.

Dose effects. The dosing conditions produced significant differences with respect to pupil diameter, respiration rate, and skin temperature (F(2,34) < 0.95 in both cases). The 10 mg/70 kg morphine condition produced significantly greater reductions in pupil diameter relative to the 5 mg/70 kg morphine condition, which in turn produced greater reductions in pupil diameter compared with placebo. Both active doses produced changes in skin temperature different from placebo. Additionally, the 10 mg/70 kg dose produced lower respiration rates compared with the placebo condition. No other significant dose effects were observed on measures of respiration rate, oxygen saturation, pulse, systolic blood pressure, or diastolic blood pressure.

Plasma Data

Infusion rate effect. A significant effect of infusion rate was observed in peak plasma concentrations of morphine (F(2,34) = 76.9; p = < 0.0001), with the bolus infusion producing significantly higher plasma levels of morphine relative to the 15-min infusion, which in turn produced significantly higher levels relative to the 60-min infusion. No significant effect of infusion rate was observed on the peak concentrations of the morphine metabolites M6G or M3G (F(2,34) > 0.35 in both cases).

Dose effects. The active doses of morphine produced higher peak morphine plasma levels as well as higher peak levels of the metabolites M6G and M3G relative to placebo doses. Indeed, morphine levels were undetectable in all plasma samples taken under placebo conditions. The higher dose of morphine (10 mg/70 kg) produced significantly higher peak morphine plasma levels relative to the lower morphine dose (5 mg/70 kg) (F(1,17) = 42.9; p = < 0.0001). Similarly, the higher morphine dose produced significantly higher peak levels of the metabolites M6G (F(1,17) = 197; p = < 0.0001) and M3G (F(1,17) = 321; p = < 0.0001).

Time Course Effects

Figure 2 shows the time course of observed effects for several key outcome measures, including the VAS measures of drug effect, drug liking, bad, subjective agonist measure, and morphine plasma levels. As is evident by this figure, the timing of the peak effect was similar across outcome measures, including all subjective measures and plasma levels, with peak effects in both the bolus and 15-min infusion conditions occurring around 60 min in both of the active dosing conditions (the time when both of these infusions were completed). The 60-min infusion produced lower and more extended peak effects than the other two infusion rates. Moreover, as is evident in Fig. 2, most effects on these measures returned to baseline levels by the end of the 180-min observation period, although scores on these measures tended to return to baseline more slowly in the 10 mg/70 kg dosing condition compared with the 5 mg/70 kg dosing condition. Additionally, although peaking at the same time, subjective effects generally returned to baseline levels more slowly (between 150 and 180 min) than peak plasma levels (which returned to baseline levels by 90 min). Moreover, scores on the bad measure of the VAS tended to return to baseline levels more rapidly than measures of drug liking and drug effect as well as opioid agonist effects.

Discussion

The present study determined the profile of physiological, psychomotor, and self-reported effects of infusion rate of intravenously administered morphine. Four main findings were evident from the study results.

First, congruent with the hypotheses of the study, faster infusion rates of morphine produced greater positive subjective effects than slower infusion rates. This finding was evident on measures of good drug effect, drug liking, and high. Faster infusion rates also resulted in greater self-reported drug effects and opioid agonist effects, without producing significant physiological or psychomotor impairment.

A second and important finding, related to the first, was that faster infusions of drug produced significantly higher morphine plasma levels, which followed a pattern and timing of peak effect similar to the self-reported effects of the drug. Faster infusion rates of morphine could increase morphine's self-reported abuse liability in a number of ways. Although faster infusion rates of morphine may have increased drug concentrations at the µ-receptor site, the strong correspondence between the pattern and timing of peak plasma levels of morphine and the reinforcing subjective effects of the drug observed in the present study suggest that faster infusion rates produce higher blood levels and a greater rate of change in blood levels (analogous to the
These results suggest that subjective measures of drug liking may depend on both the rapidity and magnitude of changes in blood levels of drug, although within the doses and infusion rates studied, other physiological and psychomotor measures are not greatly affected by these changes in blood levels. That is, drug plasma concentration may be the mechanism by which infusion rate affected outcomes. These results parallel those reported by deWit et al. (1992) who found that the rate of increase in plasma levels of orally administered pentobarbital determined the subjective effects of the drug. One cannot, however, rule out a potential effect caused by achieving some threshold plasma concentration of morphine at faster infusion rates. Future research on this topic may better differentiate between the effects of infusion rate and threshold drug plasma levels with intravenously administered opiates.

The finding that faster infusions of morphine produce greater liking than slower infusions is consistent with the operant literature on reinforcement in general and drug self-administration in particular. Specifically, the delay between a stimulus and a response as well as the rate of the delivery of the reinforcement are important variables affecting the response. Indeed, introducing a delay between a response and a drug reward has been shown to weaken both the acquisition and maintenance of drug self-administration (Schuster, 1990).

This same interpretation may be offered to explain why different drugs within the same pharmacological class that have differing rates of onset of effects may also have differing abuse liability. For example, the barbiturate, pentobarbital, has been reported to have a higher abuse liability than the barbiturate, phenobarbital (Jasinski et al., 1978). Similarly, the benzodiazepine, diazepam, has a faster onset of effects and is also reported to have greater abuse liability than the benzodiazepine, oxazepam (Griffiths et al., 1984a,b). Moreover, this difference in onset of effect may explain, at least in part, why certain routes of drug administration (e.g., i.v.) are associated with greater abuse liability than others (e.g., oral). That is, although a given dose of a drug may be differentially absorbed when administered via different routes, it may also be metabolized at different rates and thus have a differential onset of effects (see Strang et al., 1998 for a review).

Although faster infusion rates significantly increased morphine's abuse liability in the present study, a linear effect of infusion rate was not always evident. Linear effects of infusion rate were observed on the VAS measure of drug effect and on plasma concentration levels of morphine, such that the bolus infusion produced significantly higher scores on these measures relative to the 15-min infusion, which in turn produced significantly higher scores than the 60-min infusion. Nonetheless, although the bolus infusion consistently produced significantly higher scores on all measures of self-reported drug liking compared with the 60-min infusion, the 15-min infusion did not produce effects significantly different from the bolus infusion on the VAS measures of drug liking, good, and sick or the agonist measure of the ARS. Moreover,
the 15-min infusion did not produce effects significantly different from the 60-min infusion on the VAS measures of high, bad, and sick and the LSD scale of the ARCI. These results may indicate that the three infusion rates included in the present study may have been too similar to one another and may suggest that future studies investigating infusion rate effects of morphine use a broader range of infusion rates. However, as the 15-min infusion produced similar results as the 2-min bolus infusion on key measures of drug liking, these results may also indicate that a 15-min infusion rate may be useful in detecting abuse liability in drugs that for various reasons cannot be administered at a faster rate.

The significant effect of infusion rate with intravenously administered morphine in this study contrasts with the results of the study conducted by Abreu et al. (2001) who found no significant infusion rate effect with the opiate hydromorphone when intravenously administered. The present study differed from the Abreu et al. study (2001) in several ways that may have contributed to these seemingly differential results: 1) the present study was conducted with opiate naïve individuals, unlike the earlier study which was conducted with individuals who reported experience with i.v. cocaine and heroin and 2) the present study included a broader range of infusion rates (2, 15, and 60 min), unlike the previous study's infusion rates of 2, 15 and 60 s. As Abreu and colleagues report, it is possible that infusion rate differences in this small range may not significantly alter hydromorphone response. That is, unlike cocaine, which is highly lipid soluble and transported rapidly to the brain, hydromorphone is more hydrophilic and accumulation at receptors may be more gradual. Thus, peak concentrations may not have been achieved at the site of action under the infusion rates used in that study. Further examination of the effects of onset of action of opiates is warranted to clarify these observed differences across these two studies examining the effects of infusion rate of opiates.

A third finding of the study was that, in addition to producing greater self-reported drug liking, faster infusion rates, particularly the 2-min bolus infusion, also produced higher self-reported ratings of bad and sick relative to slower infusion rates. Ratings on these measures tended to peak at the same time as measures of positive, self-reported drug effects; however, self-reported ratings of negative drug effects tended to return to baseline more quickly than ratings of positive drug effects. These results are not surprising in light of previous studies with healthy volunteers, which have also reported that although most individuals in this population report liking μ-opioid drug effects, they often report disliking opioid drug effects at one or more timepoints (Zacny et al., 1993, 1994a; Petry et al., 1998; Walker and Zacny, 1999). These results may be due to a lack of tolerance to opioid effects in these largely opioid-naïve individuals; however, faster infusion rates may produce higher ratings of bad drug effects irrespective of tolerance, which are more transient than ratings of drug liking. An empirical examination of this issue with a nonopioid naïve population would aid in clarifying this issue. Nonetheless, collecting data from non-opioid-dependent individuals is important, as the majority of individuals who may be prescribed opioids for pain relief, such as morphine, are probably from this population.

A fourth main finding of the study was the replication of previous findings demonstrating that morphine produces dose-dependent increases in self-reported reinforcing drug effects, opioid agonist effects, and morphine plasma levels (Petry et al., 1998; Heishman et al., 2000). Moreover, higher morphine doses produced greater psychomotor impairment than lower doses.

The results of the present study suggest that the abuse liability of a drug may be a joint function of both the dose of the drug and the infusion rate of the drug. Specifically, larger doses produced greater subjective liking of morphine, and faster infusions produced increases in drug effect that are similar to those produced by increases in drug dose. No interaction was detected between infusion rate and dose. Thus, there was evidence that the effects of infusion rate and dose were additive, and indeed the data obtained in the study suggest that these factors are additive and that the pharmacokineti properties of a drug, including the dosage administered and the infusion rate at which it is administered may function to jointly affect the abuse liability of the drug. This finding is similar to that reported by Balster and Schuster (1973) who found that changes in responding for cocaine were a direct function of the ratio of unit dose to infusion rate. Results of the present study suggest that this same relationship between dose and infusion rate may be similar with an opiate drug.

In sum, the present study provides empirical evidence to support the commonly held belief that the rate of onset of a drug’s effects contributes to its abuse liability. The present study expanded the published literature on this topic by demonstrating this phenomenon with intravenously administered morphine, the opiate drug that is most widely prescribed as an analgesic. Study results suggest that the various pharmacokineti properties of a drug, including the dosage administered and the infusion rate at which it is administered, may function to jointly affect the abuse liability of the drug.

Acknowledgments

We thank the Investigational Drug Pharmacy at the Fletcher Allen Health Care Hospital for medication preparation. We thank Quintiles AB, Uppsala, Sweden for performing all plasma analyses for this study.

References


Address correspondence to: Dr. Lisa A. Marsch, University of Vermont, Department of Psychiatry, Substance Abuse Treatment Center, 1 South Prospect Street, Room 1415, Burlington, VT 05401. E-mail: lisa.marsch@uvm.edu