Subjective, Psychomotor, and Physiological Effects of Cumulative Doses of Opioid μ-Agonists in Healthy Volunteers

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ABSTRACT

The subjective, psychomotor, and physiological effects of three opioid μ-receptor agonists were studied in healthy volunteers using a cumulative-dosing procedure. Sixteen volunteers with no history of drug abuse received i.v. injections of saline (SAL), morphine (MOR), hydromorphone (HM), or meperidine (MEP) in a randomized double-blind crossover design. Subjects received one injection/h for the first 4 h, and a 3-h recovery period followed. SAL was injected first during each session, then SAL or increasing doses of each drug were administered every hour for the next 3 h. The absolute doses per injection were MOR: 2.5, 5, and 10 mg/70 kg; HM: 0.33, 0.65, and 1.3 mg/70 kg; and MEP: 17.5, 35, and 70 mg/70 kg. These injections resulted in cumulative doses of MOR: 2.5, 7.5, and 17.5; HM: 0.33, 0.98, and 2.28; and MEP: 17.5, 52.5, and 122.5 mg/70 kg. Subjects completed mood forms and psychomotor tests, and physiological measures were recorded at various times after each injection and during recovery. MEP tended to produce the most intense effects immediately after drug injection, which dissipated rapidly. MOR produced the mildest effects but was associated with unpleasant side effects during recovery and after the session. HM’s effects were stronger than MOR’s, and the recovery from HM was slower than with MEP. None of the opioids produced consistent effects that are typically associated with abuse liability. Orderly dose-response functions suggested that our cumulative-dosing procedure is an efficient way of determining dose-response functions for multiple opioids within the same subjects within the same study.

Research in our laboratory has sought to characterize the subjective, psychomotor, and physiological effects of opioids in healthy, normal volunteers with no history of drug abuse (Zacny et al., 1992; 1993; 1994a, b; 1997a, b; 1998). Through randomized, double-blind, placebo-controlled crossover designs, dose-response curves have been constructed that include doses of opioids that are typically prescribed for pain relief. We have characterized the subjective, psychomotor, and physiological effects of a variety of opioid agonists [morphine (MOR), codeine, meperidine (MEP), fentanyl] and opioids with mixed actions (buprenorphine, butorphanol, nalbuphine, pentazocine) in different studies. These studies consisted of four to five sessions in which a placebo and different doses of the opioid were tested, one dose per session. This single-dosing method allows the effects of a range of doses of one drug to be studied within the same individual.

However, the method does not easily allow for dose-response curves to be constructed for multiple drugs within the same subjects because a single-dosing study would require numerous sessions to test a range of doses of three or four drugs. Because we administer opioids no more than once per week, such a study would require months to conduct, and subject recruitment and retention would be problematic. In addition, the ethics of exposing healthy volunteers to different opioids on many occasions are questionable.

In the present study we sought to characterize the effects of a range of doses of three full μ-agonists, MOR, hydromorphone (HM), and MEP, within the same subjects using a cumulative-dosing procedure. Cumulative dosing allows the effects of different doses of a drug to be assessed within the same session. First, the effects of a small dose are assessed early in the session. Then more drug is added periodically to determine the effects of larger doses (cumulative doses, or total amount of drug administered up to that point). This procedure allows an entire dose-response curve to be constructed in one session. By using this procedure, dose-response curves can be determined for several different drugs (plus placebo) within the same subjects in one study. Cumulative dosing has been used for many years in behavioral research.
pharmacology to generate dose-response functions rapidly in both nonhumans (Wenger, 1980; Winger et al., 1989) and humans (de Wit et al., 1989; Preston and Bigelow, 1993). Besides the efficiency of the procedure, another advantage is that even though multiple doses of each drug are examined within the same subject, the amount of time subjects are under the influence of each drug is much less than if subjects received single weekly injections of each dose of opioid tested.

The present study examined mood, psychomotor, and physiological effects of MOR, HM, and MEP in healthy volunteers with no history of drug abuse. These opioids are commonly prescribed for pain relief, and although each acts predominantly at the µ receptor, they may produce somewhat different profiles of effects (Reisine and Pasternak, 1996). Single-dosing studies conducted in our laboratory showed that i.v. doses of MEP (17.5–70 mg/70 kg) had more intense effects on mood (e.g., increased ratings of “sedated”, “high”, “coasting or spaced out”) than did MOR (2.5–10 mg/70 kg). Inter- and intrasubject variability in ratings of drug liking was observed with both drugs: both produced ratings indicative of liking, disliking, and neutrality in different subjects and, to some extent, within the same subjects at different time points. Both opioids had mild effects on cognitive/psychomotor performance (Zacny et al., 1993, 1994a). In one of two studies examining HM effects in healthy volunteers, oral HM (1–6 mg/70 kg) did not significantly affect self-reported sedation, stimulation, or strength or liking of the drug effect (Oliveto et al., 1994). These doses did not impair performance on the Digit Symbol Substitution Test (DSST), and in another study oral HM (1 and 3 mg) produced mild performance impairment on only 1 of 14 measures of cognitive/psychomotor performance (Pickworth et al., 1997).

Our goals in the present experiment were to systematically replicate our previous studies with MOR and MEP by testing the effects of a range of doses of each opioid within the same subjects and determine the viability of our cumulative-dosing procedure as an efficient way of determining dose-response functions. We included HM because, like MOR and MEP, it is a µ agonist that is commonly prescribed for pain relief.

**Materials and Methods**

**Subjects**

Candidates who consumed at least one alcoholic drink per week were screened by a member of our research personnel. Candidates completed the SCL-90, a questionnaire designed to assess psychiatric symptomatology (Derogatis et al., 1973), the Michigan Alcoholism Screening Test (Selzer, 1971), and a health questionnaire designed to determine medical, psychiatric, and drug-use history. Subjects were excluded if they had any medical problems or a history of Axis-I psychiatric disorder (e.g., increased ratings of “sedated”, “high”, “coasting or spaced out”) than did MOR (2.5–10 mg/70 kg). Inter- and intrasubject variability in ratings of drug liking was observed with both drugs: both produced ratings indicative of liking, disliking, and neutrality in different subjects and, to some extent, within the same subjects at different time points. Both opioids had mild effects on cognitive/psychomotor performance (Zacny et al., 1993, 1994a). In one of two studies examining HM effects in healthy volunteers, oral HM (1–6 mg/70 kg) did not significantly affect self-reported sedation, stimulation, or strength or liking of the drug effect (Oliveto et al., 1994). These doses did not impair performance on the Digit Symbol Substitution Test (DSST), and in another study oral HM (1 and 3 mg) produced mild performance impairment on only 1 of 14 measures of cognitive/psychomotor performance (Pickworth et al., 1997).

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Six female and ten male healthy volunteers [mean age (range) = 25 (21–32) years] participated. Volunteers reported consuming an average of three alcoholic drinks per week (range: 1–10 drinks). Four volunteers currently smoked marijuana (mean = 1 cigarette/week). Nine volunteers reported prior use of cannabinoids, two volunteers had used stimulants [amphetamine (AMP), methamphetamine], three volunteers reported use of hallucinogens [lysergic acid diethylamide (LSD), psilocin], and one volunteer had used nitrous oxide recreationally. Regarding lifetime use of opioids, six volunteers reported use of prescribed opioids (codeine, hydrocodone, oxycodone), and four more had been prescribed “painkillers”, the classes or names of which they could not report.

Subjects signed a written consent form that described the study in detail. The consent form stated that the drugs to be used in the study were drugs commonly used in medical settings and could come from one of six classes: sedative, stimulant, opiate, general anesthetic (at subanesthetic doses), alcohol, or placebo. Subjects underwent a resting-state electrocardiogram and a medical examination and were excluded if they had experienced any adverse reactions to general anesthetics or had pulmonary, renal, hepatic, or cardiac disorders. Urine samples were analyzed by the Cloned Enzyme Donor Immunoassay Technique (Boehringer Mannheim Corp., Indianapolis, IN) for the presence of acetaminophen, alcohol, AMPs, barbiturates, benzodiazepines, cocaine metabolites, opiates, phencyclidine, and salicylates. Subjects were told not to consume any drugs, including prescription and over-the-counter medication, for 24 h before each session. Urine samples and blood-alcohol levels (as measured by a breath intoximeter) collected before each session ensured drug and alcohol abstinence. Subjects practiced mood and psychomotor tests during an orientation session. Payment was made at a debriefing session and the study was approved by the local Institutional Review Board.

**Procedure**

**Experimental Design.** A randomized, placebo-controlled, double-blind crossover trial was conducted. Subjects participated in four sessions spaced at least 1 week apart. Sessions were approximately 7.5 h in duration. During each session subjects received absolute doses (actual amount of drug injected) of i.v. MOR (0, 2.5, 5, and 10 mg/70 kg), HM (0, 0.33, 0.65, and 1.3 mg/70 kg), MEP (0, 17.5, 35, and 70 mg/70 kg), or saline (SAL; placebo). The cumulative doses of opioid, therefore, were MOR (0, 2.5, 7.5, and 17.5 mg/70 kg), HM (0, 0.33, 0.98, and 2.28 mg/70 kg), and MEP (0, 17.5, 52.5, and 122.5 mg/70 kg). The doses are clinically relevant: the largest absolute amount injected was a dose that typically would be prescribed for postoperative pain relief, and the smaller absolute doses were one-half and one-fourth this dose. The doses, therefore, are considered equianalgesic, and because all three opioids have similar onsets, durations, and peaks of effects (Jaffe and Martin, 1990; Medical Economics Data Production, 1996; Reisine and Pasternak, 1996), identical injection regimens could be used for all drugs. The drugs were drawn up by one anesthetist and injected by another. The experimenter and anesthetist administering the drug were aware of the drugs under study but were blind to the actual drug being administered each session.

**Experimental Sessions.** The experiment took place in a departmental laboratory. Subjects were instructed not to eat food or drink nonclear liquids for 2 h before the session and not to use any drugs (including alcohol and medication, but excluding normal amounts of caffeine and nicotine) for 24 h before the session. Subjects delivered a urine sample for toxicology screening, and females delivered a urine sample for a pregnancy test. A breath-alcohol test was performed, and subjects signed a form that stated that they had complied with the eating, drinking, and drug restrictions described above. Subjects reclined in a semirecumbent position in a hospital bed (thus movement in the present study was minimal) and an anesthetist inserted an angiocatheter into a forearm or hand vein in the subject’s nondominant arm. Subjects wore a pulse oximeter on their nondominant arm. Blood pressure (cuff attached to dominant arm) and respiration rate were measured periodically, and heart rate and arterial oxygen saturation were monitored continuously. Subjects filled out mood forms and completed psychomotor tests before drug administration and vital signs were recorded. After this baseline (BL) period subjects were told, “The injection you are about to receive may or may not contain a drug”, and the anesthetist injected SAL through the angiocatheter. At various times after drug injection, mood, psychomotor performance, and physiological status were...
assessed. One hour after the first (SAL) injection, subjects received another injection containing the smallest drug dose (or SAL during the placebo session). Again, subjects completed mood forms and psychomotor tests, and vital signs were recorded. Subjects received two more injections in this way, with the medium and largest dose (or SAL) being injected 2 and 3 h, respectively, after the first SAL injection. Mood, psychomotor performance, and physiological status continued to be assessed for 4 h after the last injection.

Drinking water was permitted 90 min after the last injection, and lunch was provided to the subjects 2 h after the last injection. When no tests were scheduled subjects were free to engage in sedentary recreational activities, such as reading, listening to music, and watching TV, but studying was not permitted. Social interaction was possible (e.g., the subject could converse with the research technician), but subjects generally engaged in solitary activities during sessions. Subjects were transported home after sessions via a livery service with instructions not to engage in certain activities (e.g., driving, cooking, caring for children, drinking alcohol) for 12 h after the session.

**Dependent Measures**

The first injection was administered at 0 min. The timer was started after the first injection and subsequent injections were given at 60, 120, and 180 min. All dependent measures (except the postsession adjective checklist) were completed at BL (after the angi-catheter was inserted but before the first injection) and 30 min after each injection (i.e., at 30, 90, 150, and 210 min). Subjects did not have access to how they responded on previous tests and were asked to respond to mood questionnaires “according to how you feel right now”. Table 1 lists the order of testing, which remained invariant across subjects and sessions.

**Subjective Effects.** 1. The Addiction Research Center Inventory (ARCI) is a true-false questionnaire designed to differentiate among classes of psychoactive drugs (Haertzen, 1966). A computerized short form of the ARCI was used (Martin et al., 1971). It had 49 items and yielded scores for five different scales: pentobarbital-chlorpromazine-alcohol group (PCAG), sensitive to sedative effects; benzodiazepine group (BG) and AMP, sensitive to AMP-like effects; LSD, sensitive to somatic and dysphoric effects; and MOR-benzodiazepine group (MBG), sensitive to euphoric effects.

2. A locally developed Opiate Adjective Checklist (OAC) was constructed using items from an opiate adjective checklist derived from the Single Dose Questionnaire (Fraser et al., 1961) and a list reported as sensitive to the somatic and subjective effects of opiates (Preston et al., 1989). The checklist consisted of 12 items that were rated on a scale from 0 (“not at all”) to 4 (“extremely”). The items were as follows: “flushing”, “skin itchy”, “sweating”, “turning of stomach”, “numb”, “dry mouth”, “drive (motivated)”, “carefree”, “good mood”, “headache”, “noddling”, and “vomiting”. In addition to the time points listed above, the OAC was also administered 5, 15, and 55 min after each injection (i.e., at 5, 15, 55, 65, 75, 115, 125, 135, 175, 185, 195, and 235 min) and every 30 min during recovery (i.e., at 270, 330, 360, 390, and 420 min).

3. A locally developed visual analog scale (VAS) consisted of 23 100-mm lines, each labeled with an adjective. Subjects were instructed to draw a vertical mark on each line indicating how they felt at the time, ranging from 0 mm (“not at all”) to 100 mm (“extremely”). The adjectives were as follows: “stimulated (energetic)”, “high (‘drug’ high)”, “floating”, “sedated (calm, tranquil)”, “lightheaded”, “tingling”, “confused”, “drunk”, “elated (very happy)”, “nauseous”, “dizzy”, “coasting (spaced out)”, “feel good”, “feel bad”, “having pleasant thoughts”, “having unpleasant thoughts”, “having pleasant bodily sensations”, “having unpleasant bodily sensations”, “heavy or sluggish feeling”, “down (depressed)”, “difficulty concentrating”, “hungry”, and “sleepy (drowsy, tired)”. The VAS was administered at the same time points as the OAC (see above).

4. The Drug Effect/Liking (DEL) questionnaire assessed the extent to which subjects currently felt a drug effect and how much they liked or disliked the effect. Intensity of drug effect was rated on a scale of 1 to 5 (1 = “I feel no effect from it at all” ; 2 = “I think I feel a mild effect, but I’m not sure”; 3 = “I definitely feel an effect, but it is not real strong”; 4 = “I feel a strong effect”; 5 = “I feel a very strong effect”). For the measure of drug liking, subjects placed a vertical mark on a 100-mm line indicating how much they liked or disliked the drug (0 mm = “dislike a lot”, 50 mm = “neutral”, 100 mm = “like a lot”). The DEL questionnaire was administered at the same time points as the OAC and VAS.

5. Subjects were given a postsession adjective checklist to take home and were asked to complete this questionnaire 24 h after leaving the laboratory. The checklist consisted of 17 symptoms, and subjects were asked to rate each on a scale from 0 (“not at all”) to 4 (“extremely”) according to how much they had experienced the symptoms in the last 24 h. The symptoms were as follows: “skin itchy”, “headache”, “nausea”, “dry mouth”, “excessive hunger”, “excessive thirst”, “heavy or sluggish feeling”, “lightheaded”, “confused”, “down (depressed)”, “anxious”, “clumsy”, “coasting (spaced out)”, “difficulty concentrating”, “feel good”, “feel bad”, and “vomiting”.

**Psychomotor/Cognitive Performance.** The following tests were chosen because they have been used in previous opioid studies, and the specific aspects of psychomotor/cognitive performance the tests were designed to measure can be affected by opioids (Zacny, 1995).

1. The Maddox-Wing test measures relative position of the eyes in prism dipters. Some drugs, including opiates (Manner et al., 1987), cause extraocular muscles of the eye to diverge (exophoria); this divergence is considered to be an indicator of psychomotor impairment (Hannington-Kiff, 1970).

2. An eye-hand coordination test required the subject to track a randomly moving target (a circle) on the computer screen using a computer mouse (Nuotto and Korttila, 1991). The object of this test is to keep a small cross, which is controlled by the mouse, inside the moving target circle at all times as the circle moves randomly around the screen. The length of the test was 1 min. The dependent measure was the number of mistakes (i.e., number of times the distance from the cross to the center of the target circle exceeded 1 cm).

3. An auditory-reaction test measured the time required for subjects to react to an auditory stimulus (Nuotto and Korttila, 1991). Ten 50-dBA computer-generated tones were delivered at random time intervals (1–10 s) in a 1-min time period. The tone remained on until subjects depressed the spacebar on the computer keyboard or until 2 s elapsed, whichever occurred first. The mean reaction time (in seconds) was the dependent measure.

4. A logical-reasoning test measured such cognitive processes as reasoning, logic, and verbal ability. The 1-min computerized test is similar to that of the Logical Reasoning Test developed by Baddeley (1968) except for test duration (1 min versus 3 min) and presentation medium (computer versus paper and pencil). The logical-reasoning test uses five grammatical transformations (e.g., true versus false statements, use of the verb “precedes” versus the verb “follows”) on
statements about the relationship between two letters, A and B (e.g., A is preceded by B—true or false). The subject's task was to respond “True” or “False” depending on the veracity of the statement, by depressing the 1 or 0 keys, which corresponded to true and false, respectively, on the number pad. The number of statements answered correctly was the dependent measure.

5. In the DSST (Wechsler, 1958), subjects replaced a number with a corresponding symbol. The paper and pencil test was timed for 1 min, and the dependent measure was the number of symbols drawn correctly. This test evaluates changes in information-processing performance and the ability to concentrate. The DSST was administered at the same time points as the OAC and VAS.

Physiological Measures. Five physiological measures were assessed: heart rate, blood pressure, arterial oxygen saturation, respiration rate, and miosis. Heart rate, blood pressure, and arterial oxygen saturation were measured noninvasively with a Cardiocap II monitor (Datex, Tewksbury, MA). Respiration rate was assessed by the research technician who was blind to the drug being administered. The number of times the subject's chest or stomach rose and fell in 30 s was counted; this number was multiplied by 2 to get breaths per min. Miosis, or pupil constriction, is a physiological marker of opioid effects and was measured by photographing the subject's right pupil in a dimly lit room and measuring the diameter of the pupil. The pupil of one subject could not be measured in some photographs; therefore, data for miosis are from 15 subjects. In addition to the time points listed above, heart rate, blood pressure, arterial oxygen saturation, and respiration rate were recorded every 30 min during recovery (i.e., at 270, 300, 330, 360, 390, and 420 min).

Data analysis

Repeated-measures ANOVA was used for statistical treatment of the data. The means for each condition were analyzed using the factors Drug (MOR, HM, MEP, or SAL) and Time (except for the postsession questionnaire for which Drug was the only factor). Mean peak (maximum) and trough (minimum) ratings were also analyzed with repeated-measures ANOVA using Drug as the factor; BL data were excluded from this analysis. F values were considered statistically significant for $p < .05$ with adjustments of within-factors degrees of freedom (Huynh-Feldt) to protect against violations of symmetry. When significant Drug effects were obtained, Tukey post hoc testing compared the means for each condition with the others. When significant Drug $\times$ Time effects were obtained, Tukey post hoc testing compared the means for each condition with the other means at each time point.

Results

Subjective Effects

ARCI. Figure 1 shows that the three active drugs produced dose-related increases in scores on the PCAG (Drug $\times$ Time: $p < .001$, top) and LSD (Drug $\times$ Time: $p < .001$, middle) scales of the ARCI and decreases in scores on the BG scale (Drug $\times$ Time: $p < .001$, bottom) relative to SAL. HM produced statistically significant increases in PCAG scores and decreases in BG scores at the two largest doses, whereas the other drugs produced significant increases only after administration of the largest dose. In addition, the PCAG score after the largest dose of HM was statistically significantly higher than the score after the largest dose of MOR (top, asterisk). A statistically significant effect of Drug was also found for the AMP scale [$F(3,43) = 3.3, p < .05$]; however, the only significant difference revealed by Tukey post hoc testing was between the means for HM and MEP, neither of which was statistically different from SAL. No statistically significant effects were observed for scores on the MBG scale of the ARCI.

Table 2 shows mean peak and trough scores for scales of the ARCI that showed statistically significant effects of Drug. These results are in agreement with those shown in Fig. 1. That is, HM produced the highest peak PCAG score and the lowest trough BG score, and the mean peak PCAG and LSD scores for MOR were smaller than the means for HM and MEP (although the only statistically significant difference
TABLE 2
Mean peak or trough effects (± S.E.M.) that showed statistically significant (p < .05) effects of Drug when analyzed using repeated-measures ANOVA
Tukey post hoc tests identified which differences were statistically significant (p < .05). Drug doses (absolute amount injected) were HM: 0, .33, .65, and 1.3 mg/70 kg; MEP: 0, 17.5, 35, and 70 mg/70 kg; and MOR: 0, 2.5, 5, and 10 mg/70 kg.

<table>
<thead>
<tr>
<th>Dependent Measure</th>
<th>SAL</th>
<th>HM</th>
<th>MEP</th>
<th>MOR</th>
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<tbody>
<tr>
<td><strong>Subjective Effects</strong></td>
<td></td>
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<tr>
<td><strong>ARCI Scale:</strong></td>
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<td></td>
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<tr>
<td>PCAG</td>
<td></td>
<td></td>
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<tr>
<td>LSD</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>BG*</td>
<td>3.9 (0.5)</td>
<td>1.9 (0.4)</td>
<td>2.3 (0.5)</td>
<td>2.8 (0.4)</td>
</tr>
<tr>
<td><strong>OAC Adjective:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>flushing</td>
<td>0.2 (0.1)</td>
<td>1.4 (0.3)*</td>
<td>1.5 (0.3)*</td>
<td>1.4 (0.3)*</td>
</tr>
<tr>
<td>skin itchy</td>
<td>0.3 (0.2)</td>
<td>1.9 (0.4)*</td>
<td>1.1 (0.3)</td>
<td>1.8 (0.3)*</td>
</tr>
<tr>
<td>sweating</td>
<td>0.1 (0.1)</td>
<td>0.6 (0.2)*</td>
<td>0.8 (0.3)*</td>
<td>0.2 (0.1)</td>
</tr>
<tr>
<td>turning of stomach</td>
<td>0.4 (0.2)</td>
<td>1.6 (0.2)*</td>
<td>1.8 (0.3)*</td>
<td>1.4 (0.3)*</td>
</tr>
<tr>
<td>numb</td>
<td>0.3 (0.1)</td>
<td>1.4 (0.4)*</td>
<td>1.6 (0.4)*</td>
<td>1.1 (0.2)*</td>
</tr>
<tr>
<td>dry mouth</td>
<td>1.1 (0.3)</td>
<td>2.1 (0.3)*</td>
<td>2.8 (0.3)*</td>
<td>1.8 (0.3)</td>
</tr>
<tr>
<td>drive*</td>
<td>0.7 (0.2)</td>
<td>0.3 (0.1)*</td>
<td>0.3 (0.1)*</td>
<td>0.4 (0.1)</td>
</tr>
<tr>
<td>nodding</td>
<td>0.9 (0.3)</td>
<td>2.3 (0.4)*</td>
<td>1.9 (0.4)*</td>
<td>2.1 (0.4)*</td>
</tr>
<tr>
<td><strong>VAS Adjective:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>high</td>
<td>13.3 (6.5)</td>
<td>35.6 (8.3)*</td>
<td>53.1 (9.8)*</td>
<td>37.4 (8.0)*</td>
</tr>
<tr>
<td>floating</td>
<td>14.7 (7.1)</td>
<td>42.8 (8.0)*</td>
<td>51.1 (8.2)*</td>
<td>36.3 (7.1)*</td>
</tr>
<tr>
<td>sedated</td>
<td>35.4 (8.7)</td>
<td>62.2 (7.8)*</td>
<td>63.4 (6.0)*</td>
<td>52.6 (7.8)*</td>
</tr>
<tr>
<td>lightheaded</td>
<td>16.0 (7.4)</td>
<td>57.2 (7.7)*</td>
<td>64.8 (7.9)*</td>
<td>49.2 (7.4)*</td>
</tr>
<tr>
<td>tingling</td>
<td>12.8 (5.7)</td>
<td>40.4 (8.9)*</td>
<td>41.5 (8.0)*</td>
<td>39.2 (7.7)*</td>
</tr>
<tr>
<td>confused</td>
<td>15.2 (6.5)</td>
<td>29.7 (8.8)</td>
<td>37.2 (7.8)*</td>
<td>21.4 (6.7)</td>
</tr>
<tr>
<td>drunk</td>
<td>7.9 (4.2)</td>
<td>22.5 (9.3)</td>
<td>40.4 (8.7)*</td>
<td>16.9 (6.9)</td>
</tr>
<tr>
<td>nauseous</td>
<td>9.9 (5.6)</td>
<td>32.3 (7.2)*</td>
<td>48.4 (7.4)*</td>
<td>32.4 (7.9)*</td>
</tr>
<tr>
<td>dizzy</td>
<td>10.2 (4.9)</td>
<td>43.7 (8.5)*</td>
<td>63.2 (6.5)*</td>
<td>28.7 (7.7)*</td>
</tr>
<tr>
<td>coatsing</td>
<td>16.3 (7.7)</td>
<td>50.3 (8.3)*</td>
<td>52.4 (8.9)*</td>
<td>40.8 (9.0)*</td>
</tr>
<tr>
<td>feel good*</td>
<td>33.4 (5.7)</td>
<td>19.1 (5.7)*</td>
<td>19.6 (4.5)*</td>
<td>21.3 (5.2)</td>
</tr>
<tr>
<td>feel bad</td>
<td>11.0 (3.7)</td>
<td>36.9 (7.5)*</td>
<td>34.4 (6.2)*</td>
<td>27.7 (7.2)</td>
</tr>
<tr>
<td>pleasant thoughts*</td>
<td>23.0 (6.5)</td>
<td>15.8 (5.5)</td>
<td>14.9 (4.9)</td>
<td>11.9 (4.9)*</td>
</tr>
<tr>
<td>unpleasant thoughts</td>
<td>11.1 (4.3)</td>
<td>26.3 (6.2)*</td>
<td>27.4 (6.4)*</td>
<td>18.1 (4.3)</td>
</tr>
<tr>
<td>pleasant bodily sensations</td>
<td>31.9 (8.7)</td>
<td>53.3 (7.8)*</td>
<td>47.9 (7.7)</td>
<td>40.5 (8.3)</td>
</tr>
<tr>
<td>unpleasant bodily sensations</td>
<td>16.1 (4.8)</td>
<td>35.9 (8.4)*</td>
<td>43.6 (6.8)*</td>
<td>32.5 (6.6)</td>
</tr>
<tr>
<td>heavy or sluggish feeling</td>
<td>21.8 (8.0)</td>
<td>51.6 (8.6)*</td>
<td>49.1 (8.0)*</td>
<td>45.6 (8.3)*</td>
</tr>
<tr>
<td>difficulty concentrating</td>
<td>20.0 (8.2)</td>
<td>55.4 (8.8)*</td>
<td>65.6 (7.1)*</td>
<td>47.3 (7.9)*</td>
</tr>
<tr>
<td>sleepy</td>
<td>48.5 (7.5)</td>
<td>83.7 (4.2)*</td>
<td>72.4 (5.6)*</td>
<td>69.4 (6.6)</td>
</tr>
<tr>
<td><strong>DEL questionnaire:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intensity of drug effect</td>
<td>2.0 (0.2)</td>
<td>4.4 (0.2)*</td>
<td>4.7 (0.1)*</td>
<td>3.9 (0.2)*</td>
</tr>
<tr>
<td>Liking of drug effect</td>
<td>56.3 (3.0)</td>
<td>65.9 (3.8)*</td>
<td>68.5 (3.8)*</td>
<td>66.4 (3.0)*</td>
</tr>
<tr>
<td>Liking of drug effect*</td>
<td>41.5 (1.8)</td>
<td>22.0 (3.9)*</td>
<td>23.3 (3.8)*</td>
<td>29.1 (3.7)*</td>
</tr>
<tr>
<td><strong>Psychomotor Performance</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maddox-Wing (exophoria)</td>
<td>3.0 (0.6)</td>
<td>6.7 (1.1)*</td>
<td>4.4 (0.8)</td>
<td>5.7 (1.1)*</td>
</tr>
<tr>
<td>Coordination (mistakes)</td>
<td>17.4 (1.0)</td>
<td>25.5 (1.5)*</td>
<td>23.3 (1.5)*</td>
<td>20.2 (1.4)</td>
</tr>
<tr>
<td>DSST (correct symbols)</td>
<td>44.9 (1.8)</td>
<td>32.4 (2.3)*</td>
<td>32.2 (2.7)*</td>
<td>36.8 (2.1)*</td>
</tr>
<tr>
<td><strong>Physiological Effects</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pupil diameter (mm)*</td>
<td>5.5 (0.2)</td>
<td>3.1 (0.2)*</td>
<td>4.3 (0.2)*</td>
<td>3.3 (0.3)*</td>
</tr>
<tr>
<td>Breaths per min*</td>
<td>13.0 (0.9)</td>
<td>11.0 (0.7)*</td>
<td>11.6 (0.6)</td>
<td>10.8 (0.5)*</td>
</tr>
</tbody>
</table>

*a: Trough score rating analyzed.
*b: Statistically significantly different from SAL.
*c: Statistically significantly different from MOR.
**: Statistically significantly different from MEP.

was between PCAG scores for HM and MOR). The trough BG score for HM and MEP was statistically lower than that for SAL, but the trough BG score for MOR was not statistically different from SAL.

**OAC.** Statistically significant Drug × Time interactions were found for seven of the twelve adjectives on the OAC: “flushing” (p < .001), “skin itchy” (p < .001), “turning of stomach” (p < .001), “numb” (p < .001), “dry mouth” (p < .001), “drive (motivated)” (p < .005), and “nodding” (p < .001). Ratings of “drive” decreased and ratings of the other adjectives increased in a dose-related manner after administration of all opioids. These effects were similar for all active drug conditions, except for ratings of “skin itchy” and “dry mouth”. Figure 2 shows that HM had the largest effect and MEP had the least effect on ratings of “skin itchy” (left). HM-induced increases at the 235-min time point were statistically higher than ratings after both MEP and MOR administration, and ratings at several other time points (210, 270, 300, and 330 min) were statistically higher than ratings after MEP. Figure 2 also shows that MEP had the largest effect on ratings of “dry mouth” (right) relative to HM and MOR, which produced similar, smaller increases in ratings. A statistically significant effect of Drug was found for ratings of “sweating” (p < .05). HM and MEP increased ratings of “sweating”, and MOR had no effect.

Mean peak and trough ratings of adjectives on the OAC (Table 2) are concordant with these results. That is, adjectives that showed statistically significant Drug effects or Drug × Time interactions also showed statistically significant effects of Drug when peak or trough ratings were analyzed. For example, Table 2 shows that peak ratings of “skin itchy” after HM administration were statistically higher than ratings after MEP administration, and peak ratings of “dry mouth” were statistically higher after MEP administration.
relative to both HM and MOR. HM and MEP produced similar increases in ratings of sweating, and MOR had no effect. Mean peak ratings for the other adjectives listed were significantly different from SAL (except ratings of “drive” after MOR) but not from each other.

VAS. Statistically significant Drug × Time interactions were observed for 16 of the 23 adjectives on the VAS: “stimulated (energetic)” (p < .01), “high (‘drug’ high)” (p < .001), “floating” (p < .001), “sedated (calm, tranquil)” (p < .005), “lightheaded” (p < .001), “tingling” (p < .01), “confused” (p < .05), “dizzy” (p < .005), “nauseous” (p < .001), “coasting (‘space out’)” (p < .001), “feel good” (p < .05), “difficult concentrating” (p < .001), “high” (p < .001), and “sleepy (drowsy, tired)” (p < .001). Average ratings for these adjectives increased after administration of active drugs except ratings of “feel good”, “stimulated”, and “hungry”, which decreased relative to ratings after SAL administration. Figure 3 shows average ratings of “dizzy” (top left) and “high” (top right). MEP produced the largest increases in ratings of these adjectives, and these effects tended to dissipate almost to BL levels within 15 to 55 min after each injection. A similar pattern was observed for ratings of “floating”, “lightheaded”, “confused”, “dizzy”, “nauseous”, “coasting”, and “difficulty concentrating”. In general, for these latter adjectives, including “dizzy” and “high”, MOR tended to produce smaller increases, or increases at fewer time points, than did HM or MEP.

Self-reported nausea (Fig. 3, bottom left) after MEP was highest 5 min after injection of the two largest doses and tended to recover within 1 h. In contrast, mean ratings of “nauseous” after both MOR and HM administration were lower during drug administration periods than during the recovery period: a statistically significant increase relative to placebo was observed at only the 330-min time point for HM and not until the 420-min time point for MOR. MOR appeared to have the smallest effect on ratings of “sedated” and “tingling”, with MEP increasing ratings of “sedated” at smaller doses than HM. In addition, ratings of “hungry” after MOR were not statistically different from ratings after SAL, and subjects tended to report being least hungry after MEP administration. HM produced the largest increases in ratings of “sleepy” relative to both MOR and MEP (Fig. 3, bottom right), and ratings of “heavy/slow” were increased at more time points after HM than after MOR or MEP. All opioids decreased ratings of “feel good” and “stimulated” to a similar extent.

A main effect of Drug was observed for ratings of “having unpleasant bodily sensations” (p < .05), and the Drug × Time interaction for ratings of “feel bad” approached statistical significance (p < .10). HM and MEP administration increased ratings of these adjectives to a greater extent than did MOR. Increases after MEP administration were attenuated soon (15–55 min) after each injection, whereas HM and MOR tended to produce the largest increases during the recovery period, up to 4 h after the last injection.

Mean peak and trough ratings for adjectives on the VAS are shown in Table 2. These results are consistent with those reported above, but some discrepancies exist. In general, MOR tended to produce the smallest mean peak ratings for most adjectives; however, in many cases, the differences between MOR and the other opioids were not statistically significant. This pattern of results is concordant with results based on the ANOVA’s using Drug and Time as factors. Results that are discordant include the fact that although ratings of “stimulated” and “hungry” showed statistically significant Drug × Time interactions, mean peak and trough ratings did not show significant effects of Drug. Peak ratings of “unpleasant thoughts” and “pleasant bodily sensations” and trough ratings of “pleasant thoughts” showed statistically significant differences, even though no statistically significant Drug or Drug × Time effects were observed for mean ratings of these adjectives. Although the time course of self-reported nausea differed across drug conditions and although MEP produced larger increases than HM or MOR (Fig. 3, bottom left), peak ratings of nausea were not statistically significant.
significantly different after administration of the different opioids.

DEL Questionnaire. The three opioids increased ratings of intensity of the drug effect in a dose-related manner (Drug × Time; \( p < .001 \)). MOR-induced increases were slightly (but statistically significantly) smaller at some time points than HM- and MEP-induced increases (at 125 min compared with HM, and at 125, 135, and 185 min compared with MEP). Table 2 shows that the peak rating of intensity of the drug effect was higher after HM and MEP than after MOR. MEP’s effects on this measure dissipated more quickly during the recovery period than did the effects of HM and MOR.

No statistically significant Drug × Time interactions were observed for the measure of drug liking; however, when peak and trough ratings of drug liking were analyzed by repeated-measures ANOVA (Table 2), a statistically significant effect of Drug was observed. Tukey post hoc tests revealed that mean peak and trough ratings for all opioids were significantly different from SAL but not from each other. Inspection of data for individual subjects revealed some intersubject variability in that three subjects reported consistent disliking of all three opioids, and the other 13 subjects reported both liking and disliking of opioid effects. It is interesting to note that no subjects reported consistent liking of the three opioids tested. Of the 13 subjects who reported both liking (ratings higher than 60 mm on the VAS) and disliking (ratings lower than 40 mm on the VAS) of opioid effects, there was considerable variability in the within-session pattern of liking ratings and in the number of time points within a session in which opioid effects were reported as being liked versus disliked. No obvious differences in extent of drug liking/disliking for different opioids were observed, either in the peak/trough analysis or in visual inspection of individual graphs.

Postsession Adjective Checklist. Statistically significant Drug effects were found for ratings of 4 of the 17 adjectives on the postsession adjective checklist: “feel bad” (\( p < .05 \)), “heavy or sluggish feeling” (\( p < .05 \)), “nausea” (\( p < .01 \)), and “skin itchy” (\( p < .05 \)). MOR produced the only statistically significant increases relative to SAL on these four adjectives. Results for three other adjectives approached statistical significance (\( p < .10 \)): “difficulty concentrating”, “lightheaded”, and “vomiting”. For these adjectives, also, MOR produced the largest increases. Four people reported vomiting after the session in which MOR was administered. One of these subjects vomited after the HM session, and another vomited after the MEP session. In general, then, MOR appeared to produce longer-lasting unpleasant effects than HM or MEP.

Psychomotor/Cognitive Performance

Statistically significant Drug × Time interactions were observed for Maddox-Wing (\( p < .001 \), eye-hand coordination.
(p < .001), and DSST (p < .001) performance. Dose-related exophoria was observed for HM and MOR; MEP did not induce exophoria. All opioids produced dose-related increases in the number of mistakes on the eye-hand coordination test at the largest dose. MOR produced the smallest increases, and HM impaired coordination to the greatest extent in that it also impaired performance at the second largest dose. Figure 4 shows the average number of symbols drawn correctly on the DSST. Dose-related decreases were observed for all drugs, with MOR producing the smallest decreases. MEP impaired DSST performance to the largest extent 5 min after the last two injections; this impairment was attenuated more quickly than the effects of MOR and HM, which continued up to 210 min after the last injection (i.e., at the 390-min time point). Results for the auditory reaction time test approached statistical significance (p < .10), with MOR producing smaller increases in reaction time than the other opioids. No statistically significant differences occurred for results of the logical reasoning test.

Mean peak impairment is shown in Table 2 for psychomotor measures that showed statistically significant effects of Drug on mean peak or trough scores. These data are similar to the results described above. That is, HM produced the highest peak exophoria score, and the peak after MEP administration was not statistically different from SAL. The maximum number of mistakes on the eye-hand coordination test induced by MOR was not significantly different from SAL, but the peaks for HM and MEP were. Although the trough values for number of symbols drawn correctly on the DSST were lower for HM and MEP, these values were not significantly different from MOR.

**Physiological Measures**

Figure 5 shows that pupil diameter decreased as a function of dose administered (Drug \times Time: p < .001) and that MOR and HM produced more miosis than MEP. A statistically significant Drug \times Time interaction was also observed for pulse (p < .05) and respiration rate (p < .05). However, only one time point for pulse and four time points for respiration rate showed statistically significant differences relative to SAL, and only one of these differences was clinically significant (at least 20% difference from SAL): the respiration rate at the 330-min time point during the MOR condition was 20.2% lower than the rate at the 330-min time point during the SAL condition.

Trough effects for respiration rate and miosis are shown in Table 2. MEP produced the least miosis by this measure, also; mean trough effects of HM and MOR, which were similar, were statistically lower than the mean value for MEP. HM and MOR produced similar mean trough respiration rates, and the trough respiration rate for MEP was not statistically different from SAL.

**Discussion**

Orderly dose-response functions were observed for subjective, psychomotor, and miotic effects; therefore, our cumula-
tive-dosing procedure appears to be an effective way to determine dose-response functions for opioids in healthy volunteers within a single session. In general, MOR tended to produce the mildest effects on mood and psychomotor performance relative to HM and MEP. These results replicate those found in previous single-dosing studies conducted in our laboratory, in that mood effects noted with MEP (Zacny et al., 1993) were more intense than those observed in other studies with MOR (Zacny et al., 1994a, b; 1997a, b; 1998). Psychomotor impairment in these previous studies was modest at best, with MOR and MEP producing either no or slight impairment. In the present study psychomotor performance was more impaired than in these other studies, a result that is not unexpected, given that although we tested identical doses in the present study, we administered them an hour apart (rather than in separate sessions) such that, because effects of the previous dose had not completely worn off before the next dose was injected, the largest doses tested in the present study (the cumulative doses) were probably larger than the largest doses tested in the single-dosing studies. It is not surprising, therefore, that milder effects were observed in the single-dosing studies compared with the present one. In the only studies that have examined HM effects in healthy volunteers, almost no effects on mood and psychomotor performance were observed, and those that were reported were mild (Oliveto et al., 1994; Pickworth et al., 1997). These studies tested 1 to 6 mg oral HM; however, 7.5 mg is the oral dose thought to be equianalgesic to the largest dose injected in the present study (1.3 mg/70 kg i.v. [cumulative dose = 2.28 mg/70 kg]; Jaffe and Martin, 1990). Therefore, the milder effects observed in those studies compared with the present one may be due to the smaller doses tested and/or the route of administration.

Some differences were observed in the patterns of subjective effects of different opioids. MEP appeared to be the most “intoxicating” of the opioids, in that it produced the largest mean peak ratings of “high”, “floating”, “confused”, “drunk”, “coasting”, and “difficulty concentrating”. These more intense effects were short-lived, however; they peaked 5 min after drug injection and recovered, sometimes to BL levels, within 55 min. A number of effects of HM and MOR peaked 15 to 55 min after an injection, and recovery was slower than with MEP. Given that the onset of analgesia is slightly faster and the duration of analgesia is slightly shorter for MEP than for HM and MOR (Jaffe and Martin, 1990; Medical Economics Data Production, 1996), these differences in time course of subjective effects are not entirely unexpected. The present data point to the importance of assessing dependent measures at multiple time points shortly after drug administration, as well as assessing them for a prolonged period of time (i.e., recovery). Omission of the dependent-measures assessment 5 min after each injection would have made MEP’s peak effects appear smaller. Testing during the recovery period revealed that HM and MOR continued to produce “unpleasant” subjective effects (increased ratings of “unpleasant bodily sensations”, “feel bad”, and “nauseous”) for 4 h after the last injection. Our postsession questionnaire also revealed that MOR continued to have “unpleasant” effects (increased ratings of “feel bad”, “heavy or sluggish”, “nausea”, “skin itchy”, “vomiting”) even after subjects left the laboratory, and Seever and Pfeiffer (1936) also found more prolonged side effects of MOR compared with HM in normal volunteers (see also Lasagna et al., 1955). Although MOR appeared to produce the mildest subjective and psychomotor effects during the 4-h drug-administration/testing period, it continued to have “negative” effects, which occurred into the recovery (as did HM’s) and postsession periods.

MEP had the mildest effect on ratings of “skin itchy” and on miosis and the greatest effect on ratings of “dry mouth”. Woodhouse et al. (1996) also found that patients given MEP reported being less itchy than patients given MOR, and Rapp et al. (1996) found that patients receiving MOR or HM reported similar levels of itchiness. In the present study, HM appeared to increase self-reported itchiness to a greater extent than MOR; however, the difference in means for MOR and HM was statistically significant at only one time point (Fig. 2, left), and the peak ratings were not significantly different (Table 2). In a study with former opiate abusers (Jasinski and Preston, 1986) and in the single-dosing study by Zacny et al. (1993), MEP was less potent in inducing miosis than it was in inducing MOR-like subjective effects (see also Jasinski and Nutt, 1973), a result that is consistent with results of the present study. That is, the same doses of MEP that produced more intense subjective effects than equianalgesic doses of MOR also produced less miosis. MEP is known to have anticholinergic properties (Batterman, 1943; Wynn et al., 1990), and these properties may account for MEP’s lesser effect on pupil diameter (Mansky, 1978; Clark et al., 1995) and its greater effect on ratings of “dry mouth” (Parrott, 1986; Sannita et al., 1987; Zacny et al., 1993).

Inter- and intrasubject variability in extent of drug liking was observed in the present study and has been reported in previous opioid studies with healthy volunteers who have no history of opioid dependence (Lasagna et al., 1955; Zacny et al., 1992, 1993, 1994a). In contrast with subjects with a history of opioid dependence, who consistently report “pleasant” effects of μ-agonist opioids (Jasinski and Nutt, 1973; Jasinski et al., 1977; Jasinski and Preston, 1986; Preston and Bigelow, 1993, 1994; Strain et al., 1993), subjects in the population we sample do not consistently report pleasant effects, and indeed may report unpleasant effects or a disliking of the drugs. Zacny et al. (1994a) found that about half the subjects tested with MOR 2.5, 5, and 10 mg/70 kg reported liking effects of 5 and 10 mg/70 kg at one or more time points, and four of these six subjects first liked then disliked the effects (i.e., biphasic response). In the study with MEP 17.5, 35, and 70 mg/70 kg, about half the subjects liked the two large doses of MEP within 45 min of the injection; however, half reported neutrality toward or disliking of the drug effects at these time points (Zacny et al., 1993). Seever and Pfeiffer (1936) reported that although one of their subjects became euphoric after drug administration, none of the subjects (N = 8) expressed a “desire for repetition” of the procedures, which included i.m. and s.c. MOR 8 mg and HM 1 mg. Similarly, s.c. MOR 8 and 15 mg and heroin 2 and 4 mg produced more reports of “unpleasant” than “pleasant” effects, and reports of “unpleasant” effects increased with increasing dose (Lasagna et al., 1955). In the present study, although 10, 12, and 11 subjects reported liking MOR, HM, and MEP, respectively, at one or more time points, 12, 14, and 13 subjects, respectively, also expressed a disliking of these drugs at one or more time points. These opioids, then, were at least as likely to produce disliking as liking. In
addition, other dependent measures that are putatively associated with abuse liability (MBG scores on the ARCI, ratings of “carefree,” “good mood,” “elated”) showed no statistically significant Drug or Drug × Time effects, and ratings of “feel good” decreased after drug administration relative to SAL. The present results are in agreement with the studies described above and suggest that although opioid agonists can induce drug liking in healthy volunteers, they do not consistently increase ratings of drug liking or other effects thought to be associated with abuse potential in people with no history of drug abuse. Data from this population are important to collect because it is this population that makes up the majority of people who will be prescribed these drugs for pain relief.

In most cases, results of both time course and peak/trough analyses were concordant; for example, based on the time course data, MEP appeared to produce the largest maximum increases in VAS ratings of “dizzy” and “high” (Fig. 3, top), and peak effects were also statistically higher for MEP than for HM or MOR (Table 2). MEP appeared to have the least effect on pupil diameter when either time course (Fig. 5) or trough (Table 2) effects were analyzed. Several other dependent measures showed a concordance in results of the two types of analyses (e.g., ARCI scores, ratings of several OAC and VAS adjectives, exophoria, eye-hand coordination, DSST performance). In other cases, results of the two analyses were discordant. For example, MOR appeared to have the least effect on several subjective-effects measures when Drug × Time effects were analyzed, but in many cases, no statistically significant differences in peak or trough effects were observed among active-drug conditions (e.g., VAS ratings of “floating,” “lightheaded”). No statistically significant differences in peak effects of the opioids were revealed by Tukey post hoc testing for ratings of “nauseous” (Table 2), even though examination of the means of all time points suggests that MEP produced the largest maximum effect (Fig. 3, bottom left). This type of result suggests that the drugs did not differ so much in their maximum effect on ratings of “nausea” (and several other dependent measures) as might be suggested by the Drug × Time analysis and that inclusion of both types of analysis results in a more complete characterization of opioid effects.

In summary, our cumulative-dosing procedure appears to be an effective methodology for determining dose-response functions for an opioid within a single session. Some studies that have compared the results of cumulative and noncumulative dosing have found similar dose-response curves (Wenger, 1980; McMillan et al., 1982), but others have found differences in results of the two procedures (Winger et al., 1989; Clark et al., 1990; Gauvin et al., 1997), indicating apparent within-session sensitization or tolerance during cumulative dosing (Thompson et al., 1983). We do not know whether sensitization or tolerance occurred in the present study because we did not compare directly the effects of cumulative versus noncumulative dosing. However, we found no apparent indication of either, given the orderly, dose-related effects that were observed and the fact that these effects were at least as strong as those observed in the single-dosing studies with MEP and MOR (Zaeny et al., 1993, 1994a). The present procedure seems ideal for characterizing effects of multiple opioids within the same study in which different doses of each drug are to be tested. Inclusion of multiple doses of each drug to be compared is imperative because relying on effects of only one dose results in an incomplete characterization and limits the generality of results.

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