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ORIGINAL INVESTIGATION

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Comparing the subjective, psychomotor, and physiological effects of intravenous hydromorphone and morphine in healthy volunteers

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Abstract *Rationale:* The psychopharmacological profile of hydromorphone, an opioid that has been used extensively for many years for post-operative pain management, has not been adequately characterized in non-drug abusers. *Objectives:* To characterize the subjective, psychomotor, and physiological effects of a range of single doses of hydromorphone in non-drug-abusing volunteers and to compare the effects of hydromorphone with that of morphine, a benchmark mu opioid agonist. *Methods:* Subjects in a six-session study were injected in an upper extremity vein with 0, 0.33, 0.65, 1.3 mg/70 kg hydromorphone, and 5 and 10 mg/70 kg morphine, using a randomized, double-blind, crossover design. *Results:* Hydromorphone increased scores on the pentobarbital-chlorpromazine-alcohol group and lysergic acid diethylamide scales and decreased scores on the benzedrine group scale of the Addiction Research Center Inventory, increased adjective checklist ratings of ("dry mouth", "flushing", and "nodding", and increased visual analog scale ratings indicative of both pleasant (e.g., drug liking) and unpleasant (e.g., "feel bad") effects. The subjective effects of morphine at putatively equianalgesic doses to those of hydromorphone were similar to those of hydromorphone, but in some cases of lesser magnitude. Psychomotor impairment was modest with hydromorphone and absent with morphine. Both opioids produced dose-dependent decreases in pupil size. A relative potency analysis indicated that hydromorphone was 10 times as potent as morphine (1 mg hydromorphone=10 mg morphine). *Conclusions:* The results of this study demonstrate that 0.33–1.3 mg hydromorphone had orderly, dose-related effects on subjective, psychomotor, and physiological variables, and similar effects to those of a benchmark mu opioid agonist, morphine.

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Introduction

Hydromorphone, also known as dihydromorphenone or Dilaudid, is a semi-synthetic derivative of morphine and a full mu-agonist opioid. It has been used for many years in the management of post-operative pain (cf. Mahler and Forrest 1975). Hydromorphone is also used in the treatment of chronic malignant pain (Houde 1986; Katcher and Walsh 1999). Jasinski et al. (1977) and a number of studies by Preston and her associates (Bickel et al. 1989; Preston et al. 1989, 1992; Preston and Bigelow 1994) have characterized the subjective effects of hydromorphone (subcutaneously and intramuscularly) in doses ranging from 1.5 to 6.0 mg/70 kg in opioid abusers. Generally in a dose-related manner, hydromorphone increased scores on the morphine-benzedrine group (MBG) scale of the Addiction Research Center Inventory (ARCI) and increased single dose questionnaire (SDQ) and opiate adjective checklist ratings of high, drug liking, and good effects. Despite robust increases in ratings of subjective effects, hydromorphone does not impair psychomotor functioning in opioid abusers (e.g., Preston et al. 1989, 1992; Preston and Bigelow 1994).

The effects of hydromorphone have also been studied in non-drug-abusing humans. Clinical studies have indirectly examined the psychopharmacological profile of hydromorphone by documenting what side effects are reported after administration of the drug. In these studies, the side effects reported have included dizziness, sedation, nausea, vomiting, and pruritus (Houde 1986; Urquhart et al. 1988; Wallenstein et al. 1990; Dunbar et al. 1996; Rapp et al. 1996). Seevers and Pfeiffer (1936), in a non-placebo-controlled experiment, compared the analgesic and subjective effects of subcutaneous and intravenous hydromorphone (1 mg), morphine (10 mg), heroin (2 mg), and codeine (64 mg) in eight healthy

males. Periodically after drug administration, subjects were asked to describe their subjective sensations resulting from the drugs. Subjects reported feeling mental sluggishness, dizziness, difficulty in concentrating, desire to sleep, nausea, and muscle weakness from all of the drugs. In a drug discrimination study in which oral hydromorphone (1–6 mg/70 kg) served as a test drug, no subjective effects were noted on the Addiction Research Center Inventory (ARCI) or a visual analog scale (VAS), and no psychomotor impairment was observed (Oliveto et al. 1994). Finally, we used a cumulative dosing procedure to compare effects of hydromorphone (hourly intravenous injections of 0, 0.33, 0.65 and 1.3 mg/70 kg) to two other full mu opioid agonists, morphine and meperidine (Walker and Zacny 1999). Hydromorphone increased pentobarbital-chlorpromazine-alcohol group (PCAG) and lysergic acid diethylamide (LSD) scores on the ARCI, affected ratings on a VAS and opiate adjective checklist, and impaired psychomotor performance. Morphine (0, 2.5, 5 and 10 mg/70 kg) produced similar effects to that of hydromorphone, albeit at a lesser magnitude in some cases (e.g., drowsiness).

The cumulative dosing study (Walker and Zacny 1999) provided useful information regarding differences between the three opioids, but was not designed to examine the effects of single doses of opioids. In previous studies we have characterized full mu (Zacny et al. 1992a, 1993, 1994a; Black et al. 1999) and mixed-action (Zacny et al. 1992b, 1994b, 1997a, 1997b, 1998) opioids, using a single-dosing method and testing several doses of the opioid across sessions. One opioid yet to be tested in this series is hydromorphone; we deemed it important to test this compound at single doses for two reasons. First, it is an opioid that is widely used in clinical practice for post-operative pain relief. A characterization of its effects would provide more complete information to clinicians regarding what non-analgesic effects (e.g., mood-altering effects) non-drug-abusing patients might be feeling from the drug. Second, many abuse liability studies have characterized this drug at single doses in opioid abusers (e.g., Preston et al. 1989, 1992). Because we use similar testing methodologies, the hydromorphone effects we obtain with non-drug-abusing volunteers can be compared to effects obtained in opioid abusers. Previous studies (e.g., Preston and Bigelow 1994; Zacny et al. 1997a) examining other opioids have indicated that there appear to be differences between the two subpopulations in that opioid abusers tend to show a more consistent pattern of euphorigenic effects and less psychomotor impairment than do non-drug abusers. Thus, the primary purpose of the present study was to characterize the subjective, psychomotor, and physiological effects of single doses of hydromorphone across a range of clinically relevant doses. A secondary purpose of this study was to determine the relative potency of hydromorphone to that of the benchmark full mu opioid agonist, morphine: two doses of morphine were compared to two putatively equianalgesic doses of hydromorphone. Clinical studies have established that hydromorphone is about 7–8 times as potent as morphine in producing analgesia (Hanna et al. 1962; Mahler and Forrest 1975; Keeri-Szanto 1976; Houde 1986). In the only known potency study which examined non-analgesic endpoints such as subjective effects (Jasinski et al. 1977), the potency ratio was slightly higher, i.e., 10:1.

Materials and methods

Subjects

The study was approved by the local Institutional Review Board. Participants were recruited primarily from newspaper advertisements and posters. Initial contact was made via a structured telephone interview (obtaining such data as age, sex, medical condition, self-reported use of alcohol, marijuana, cigarettes). Potential subjects who consumed at least one alcoholic drink per week, were between the ages of 21–39 years, and had obtained a high school diploma or equivalent with verbal fluency in English were scheduled for a personal interview. During the interview, the participants read the consent form, which contained detailed information about the study, completed a locally developed questionnaire detailing their medical and drug use history, completed the SCL-90, a questionnaire designed to assess psychiatric symptomatology (Derogatis et al. 1973), and completed the Michigan Alcoholism Screening Test (MAST) (Selzer 1971), which assessed the participants' alcohol usage. Participants with any psychiatric problems that were either drug- or alcohol-related problems or Diagnostic and Statistical Manual of Mental Disorders-IV Axis I psychiatric disorders (American Psychiatric Association 1994), as determined during a structured psychiatric interview, were excluded.

Potential subjects who passed the screening interview were scheduled for an orientation session prior to the start of the study. At the start of the orientation session, participants signed the written consent form. In the consent form, they were told that the intravenous drugs to be used in the study were drugs commonly used in medical settings and might come from one of six classes: sedative, stimulant, opiate, general anesthetic (at subanesthetic doses), alcohol, or placebo. Participants then received a resting-state electrocardiogram, and a physician obtained a medical history and performed an examination. Any participants who had experienced any adverse reactions to general anesthetics, or pulmonary, renal, hepatic, or cardiac problems were excluded from the study. Each participant was required to give a urine sample, upon which the cloned enzyme donor immunoassay technique (Boehringer Mannheim Corp., Indianapolis, Ind., USA) toxicology screening for acetaminophen, alcohol, amphetamines, barbiturates, benzodiazepines, cocaine metabolites, opiates, phencyclidine, and salicylates, was performed. Subjects were required to deliver a drug-free urine sample before entering the study and were told not to consume any illicit drugs during their participation. Subjects were also told not to use alcohol or prescription, or over-the-counter, medication for 24 h before each session. Mood and psychomotor tests were practiced by the participants during the orientation session in order to acclimate them to the tests and to avoid any practice effects on psychomotor testing during experimental sessions. Upon completion of the study, a debriefing session was held and payment for the study was remitted.

Three volunteers withdrew, or were withdrawn, from the study after completing at least one session, and their demographic data are not included below. Reasons for withdrawal included scheduling conflicts and noncompliance with protocol rules. One subject did complete five of the six sessions, which included all three hydromorphone sessions and the placebo session; these data were analyzed, and her demographic data are included below. Seventeen healthy volunteers, 12 males and five females, with a mean age (+SD) of 25.1 (4.6) years, completed the study. All volunteers had some prior use of recreational drugs, but none had histories indicative of dependence. Their self-reported number of alcohol

drinks consumed per week (over the last 30 days) averaged 3.8 (3.5). Seven volunteers reported smoking tobacco cigarettes (no more than six per day). Six volunteers reported using marijuana in the last 30 days. Two volunteers reported lifetime recreational use of opium less than 10 times, and one volunteer reported lifetime recreational use of Dilaudid less than 10 times. Nine volunteers reported having been prescribed opiates (reported as Percocet, Demerol, Tylenol with codeine, Percodan, morphine, and "prescription pain killers") in the past for pain relief.

Experimental design

A placebo-controlled, double-blind, incomplete Latin square, crossover trial was conducted. Participants were injected in a forearm vein with saline, 0.33, 0.65, 1.3 mg/70 kg hydromorphone, or 5, 10 mg/70 kg morphine, over a 30-s interval. The volume of drug or saline injected was always 5 cc. We chose the 5-mg and 10-mg morphine doses as comparator doses to the 0.65-mg and 1.3-mg doses of hydromorphone, respectively, because of their putative equianalgesic effects (Reisine and Pasternak 1996). Subjects participated in six sessions spaced at least 1 week apart. Sessions were approximately 360 min in duration.

Experimental sessions

The experiment took place in a departmental laboratory. A toxicology screening was required prior to the start of each session for all participants, as was a negative pregnancy test for all female participants. Subjects were also given a breath alcohol test to assure that they did not have alcohol in their systems. An angiocatheter was then inserted into the subjects' forearm vein by an anesthetist. While in a semi-recumbent position in a hospital bed, the subjects completed several subjective effects forms and psychomotor tests, and their respiration rate, heart rate, non-invasive arterial oxygen saturation, and blood pressure were monitored at baseline. Next, the anesthetist injected either morphine, hydromorphone, or saline into the angiocatheter over 30 s. Prior to the injection the subject was told, "The injection you are about to receive may or may not contain a drug." In order to preserve the double-blind nature of the study, the drug was previously drawn up by one anesthetist and administered by another. However, the injecting anesthetist was aware of the drugs involved in the study, so that if an adverse event occurred, appropriate measures could be taken to ensure the safety and well-being of the subject. At periodic intervals after the injection (see below), mood, psychomotor performance and physiological status of the subject were assessed. Drinking water was permitted 90 min after the injection, but eating was not allowed during the session. Between testing time points, subjects were free to engage in sedentary recreational activities such as reading, listening to music, and watching TV. Following completion of the sessions, subjects were transported home via a livery service with instructions not to engage in certain activities for the following 12 h (e.g., cooking, driving an automobile, caring for children, making important decisions, drinking alcohol).

Dependent measures

The following tests were completed before the injection, as well as at 15, 60, 120, 180, 240, and 300 min after the injection.

Subjective measures

The ARCI is a true-false questionnaire designed to differentiate among different classes of psychoactive drugs (Haertzen 1966). A computerized short-form of the ARCI was used (Martin et al. 1971) which had 49 items and yielded scores for five different scales: PCAG, sensitive to sedative effects; benzedrine group (BG) and amphetamine (AMP), sensitive to amphetamine-like effects; lysergic acid diethylamide (LSD), sensitive to somatic and dysphoric changes; and MBG, often described as euphoria.

A locally developed adjective checklist was constructed using items from an opiate adjective checklist [derived from the SDQ (Fraser et al. 1961)] and a list reported as sensitive to the somatic and subjective effects of opiates from the mu and mixed agonist-antagonist classes (Preston et al. 1989). The checklist consisted of 12 items (e.g., "drive (motivated)", "skin itchy", "vomiting") which the subject rated on a 5-point scale from 0 ("not at all") to 4 ("extremely").

A locally developed visual analog scale (VAS) consisted of twenty-three 100-mm lines, each labeled with an adjective (e.g., "coasting ('spaced out')", "heavy or sluggish feeling", "sleepy (drowsy, tired)". In addition to the testing time points listed above, the VAS was completed at 5, 45, 90, 105, and 210 min post-injection.

A locally developed drug effect/liking (DEL) questionnaire assessed the extent to which subjects currently felt a drug effect, on a scale of 1–5 (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"), and assessed the extent to which the subjects currently liked the drug effect on a 100-mm line (0=dislike a lot; 50=neutral; 100=like a lot). In addition to the testing time points listed above, the DEL questionnaire was completed at 5, 45, 90, 105, 150, and 210 min post-injection.

Subjects were given a locally developed adjective rating checklist to take home with them and were asked to complete it 24 h later, and to note whether or not they had any of the 17 symptoms listed on the checklist (e.g., "dry mouth", "headache", "vomiting") during the 24 h following the session. Each symptom on this post-session adjective checklist was rated on a 5-point scale ranging from 0 ("not at all") to 4 ("extremely").

Psychomotor/cognitive performance

The Maddox-Wing test measures relative position of the eyes in prism diopters. Some drugs cause extraocular muscles of the eye to diverge (exophoria), and this divergence is considered to be an indicator of psychomotor impairment (Hannington-Kiff 1970).

The digit symbol substitution test (DSST) was a 1-min paper-and-pencil test that required the subject to replace digits with corresponding symbols according to a digit-symbol code listed on the top of the paper (Wechsler 1958). The scores were the total number of symbols drawn and the number of symbols drawn correctly by the subject. Different forms of the test (i.e., different symbol-digit codes) were used each time the test was presented to the subject. The DSST evaluated changes in information processing performance and the ability to concentrate (Hindmarch 1980). In addition to the testing time points listed above, the DSST was completed at 5, 45, 90, 105, 150, and 210 min post-injection.

Four other tests were used that did not differentiate hydromorphone or morphine from placebo and will not be described in detail; these tests measured auditory reaction time (Nuotto and Korttila 1991), eye-hand coordination (Nuotto and Korttila 1991), logical reasoning ability (Baddeley 1964), and immediate and delayed free recall (Thorndike and Lorge 1944; Paivio et al. 1968).

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 non-invasively with a Merlin Model 54 monitor (Hewlett Packard, Andover, Mass., USA). Respiration rate was the number of breaths subjects took in 30 s (multiplied by 2 to get breaths/min). This was assessed by counting the number of times the subject's chest or stomach rose and fell, and was measured by one of the experimenters (J.H.) who was blind to the dose and drug being administered. Miosis, or pupil constriction, is a physiological marker

of opiate effects and was measured by photographing the subject's right pupil in a dimly lit room. Miosis was measured pre-injection, and at 15, 60, 120, 180, and 300 min post-injection.

Statistical analyses

Two sets of repeated-measures analysis of variance (ANOVA) were used for statistical treatment of the data. The first analysis (n=17) examined hydromorphone effects: factors were Dose (0, 0.33, 0.65, and 1.3 mg/70 kg) and Time (2–13 levels). The second analysis (n=16) compared peak and/or trough effects of saline, 0.65 and 1.3 mg hydromorphone, and 5 and 10 mg morphine: the single factor was Drug condition. Only post-injection values were included in this analysis, and values were determined for each subject independent of time point. F values were considered significant for $P \leq 0.05$ with adjustments of within-factors degrees of freedom (Huynh-Feldt) to protect against violations of symmetry. Tukey post-hoc testing was done on the first ANOVAs, comparing drug responses to saline at each time point, and on the second set of ANOVAs, comparing each of the five conditions to the others.

We also conducted a relative potency analysis of the two opioids. Peak and trough effect data from the 0.65 and 1.3 mg/70 kg hydromorphone doses and the 5 and 10 mg/70 kg morphine doses were analyzed using Finney's (1964) method for parallel line bioassays. Specifically, data which yielded significant (P<0.05) effects were used in these analyses. The analysis of parallel line bioassays is used to determine the relative potency of two compounds. This analysis was used to determine that the dose-response functions did not deviate from parallelism (P>0.05) and showed significant regression (the slopes of the dose-response functions were significantly different from 0, P<0.01) without preparation differences (overall effect magnitude did not differ across drugs, P>0.05).

Results

Subjective effects

ARCI

Hydromorphone. Significant Dose×Time effects were obtained on the PCAG (P<0.001), BG (P<0.05), and LSD (P<0.005) scales. In a dose-related manner, PCAG (Fig. 1, top frame) and LSD scores increased, and BG scores decreased, after the hydromorphone injection. Average scores on these scales reached their maximum (PCAG, LSD) or trough (BG) levels 60 min post-injection. Duration of effect on the LSD and BG scales did not exceed 2 h, whereas PCAG scores remained significantly different from placebo for up to 4 h following the injection.

Peak and trough effects. Table 1 presents mean peak and trough effects of all variables (including ARCI ratings) that were sensitive to hydromorphone (0.65, 1.3 mg) and/or morphine (5, 10 mg). Those variables not shown in the table were not altered by either drug, relative to

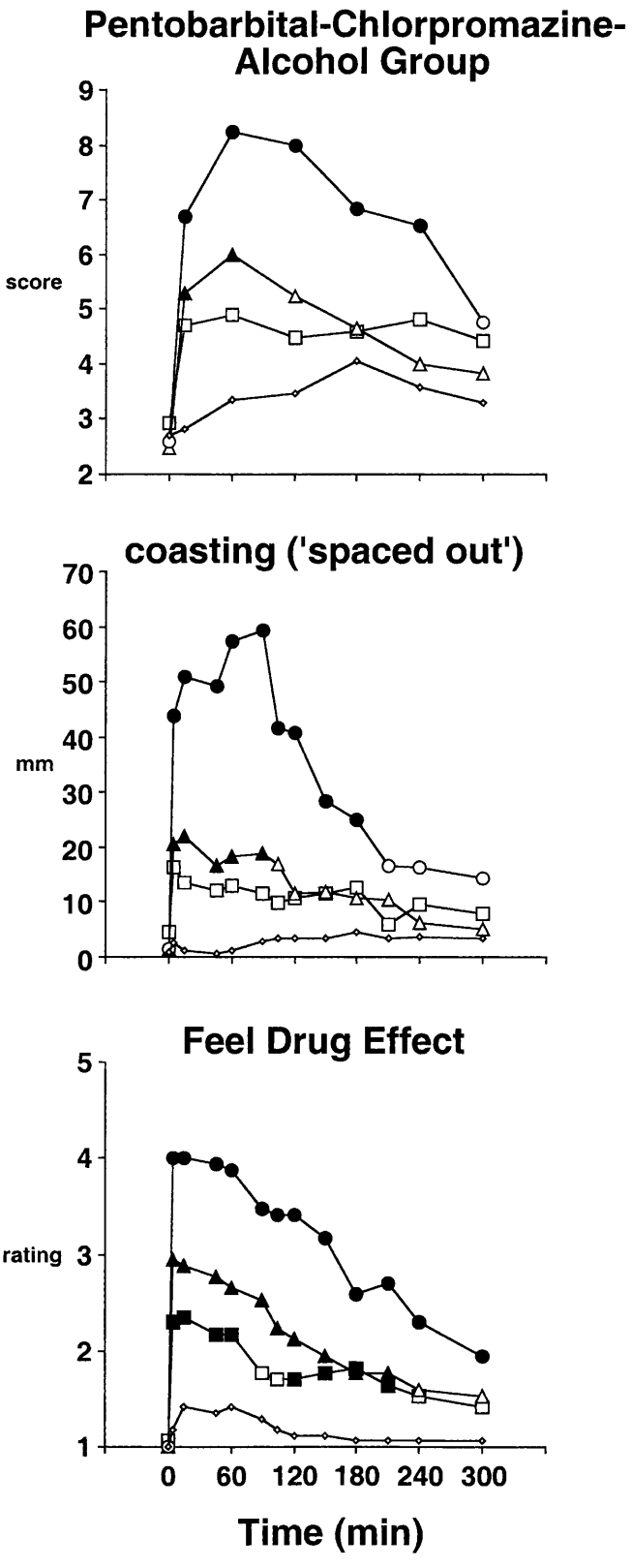

Fig. 1 Time course of the effects of hydromorphone [0 (*diamond*), 0.33 (*square*), 0.65 (*triangle*) and 1.3 (*circle*) mg/70 kg] on PCAG scores of the ARCI (*top frame*), coasting ("spaced out") ratings from the VAS (*middle frame*), and Feel Drug Effect ratings from the DEL questionnaire (*bottom frame*). Each *point* represents the mean across 17 subjects. Time point *0* refers to effects measured immediately prior to the injection. *Solid symbols* on the graphs indicate that an active dose of drug is significantly different from saline at a given time point (Tukey post hoc test; P<0.05). Range of possible scores/ratings on the PCAG, VAS, and Feel Drug Effect measures is 0–15, 0–100, and 1–5, respectively

Table 1 Mean peak or trough effects (+SEM) of dependent measures sensitive to 0.65 or 1.3 mg hydromorphone (*HM*), and/or 5 or 10 mg morphine (*MOR*)

Dependent measure	SAL	0.65 HM	1.3 HM	5 MOR	10 MOR
ARCI					
PCAG	4.8 (0.9)	6.7 (1.0)	9.2 (0.8)[a]	6.9 (0.9)	7.8 (0.8)[a]
BG[c]	4.6 (0.4)	4.5 (0.7)	2.4 (0.6)[a]	4.2 (0.4)	3.9 (0.7)
AMP	3.1(0.7)	4.1 (0.6)	4.2 (0.7)	3.8 (0.7)	4.4 (0.6)[a]
LSD	4.3 (0.4)	5.3 (0.5)	6.8 (0.6)[a]	4.6 (0.4)	5.8 (0.5)
Adjective checklist					
Flushing	0.1 (0.1)	0.2 (0.1)	0.6 (0.2)	0.1 (0.1)	0.8 (0.3)[a]
Nodding	0.2 (0.2)	1.0 (0.3)	2.0 (0.4)[a]	0.8 (0.3)	1.4 (0.3)[a]
Numb	0.1 (0.1)	0.5 (0.2)	0.6 (0.2)	0.3 (0.1)	0.7 (0.2)[a]
VAS					
Coasting	7.5 (4.1)	32.3 (7.0)[a]	73.4 (5.9)[a,b]	29.3 (7.9)[a]	50.7 (8.7)[a]
Confused	4.6 (2.9)	14.4 (5.4)	25.4 (7.6)[a]	10.6 (6.4)	15.3 (6.3)
Difficulty concentrating	7.2 (4.2)	21.4 (7.0)	49.9 (8.7)[a]	24.3 (8.5)	37.1 (8.5)[a]
Dizzy	2.4 (1.2)	19.9 (7.6)	49.1 (8.5)[a]	17.4 (7.2)	29.4 (8.0)[a]
Drunk	1.6 (0.5)	11.2 (6.0)	24.6 (7.1)[a]	7.9 (5.6)	10.3 (5.1)
Feel bad	6.6 (3.6)	14.8 (5.6)	22.8 (5.8)[a]	10.4 (4.8)	15.3 (5.0)
Floating	3.0 (1.8)	23.4 (6.4)	62.3 (7.5)[a]	25.1 (6.8)[a]	43.1 (7.5)[a]
Having pleasant bodily sensations	23.8 (7.8)	39.3 (8.1)	51.2 (8.0)[a]	37.5 (7.5)	43.1 (8.6)
Having unpleasant bodily sensations	3.6 (1.9)	26.8 (8.3)[a]	26.7 (7.0)[a]	11.1 (5.4)	14.8 (4.5)
Heavy or sluggish feeling	12.4 (5.5)	32.7 (8.4)	66.8 (7.5)[a,b]	35.3 (8.9)	36.3 (7.9)[a]
High	1.8 (0.4)	32.3 (5.5)[a]	70.7 (6.7)[a]	27.8 (8.1)[a]	50.4 (8.4)[a]
Hungry[c]	39.8 (8.8)	25.1 (6.1)	17.3 (5.6)[a]	21.4 (6.6)	14.9 (6.4)[a]
Lightheaded	6.1 (3.5)	27.4 (7.2)	61.6 (8.0)[a]	29.0 (7.7)[a]	41.1 (9.0)[a]
Nauseous	2.5 (1.1)	17.6 (7.1)	25.6 (7.7)[a]	8.6 (3.6)	15.8 (6.0)
Sedated	17.4 (5.6)	37.4 (7.5)	64.5 (6.7)[a]	38.6 (7.7)	56.6 (8.9)[a]
Sleepy	35.8 (8.4)	51.9 (8.0)	73.6 (7.6)[a]	50.9 (8.6)	53.7 (9.0)
Tingling	4.3 (1.4)	18.1 (5.8)	38.1 (8.4)[a]	18.0 (5.5)	34.5 (8.3)[a]
DEL questionnaire					
Intensity of drug effect	1.4 (0.2)	3.3 (0.2)[a]	4.3 (0.2)[a]	3.2 (0.2)[a]	3.8 (0.2)[a]
Liking of drug effect	52.5 (0.8)	65.5 (3.5)[a]	71.9 (4.3)[a]	65.6 (3.6)[a]	70.8 (3.6)[a]
Psychomotor performance					
Maddox-Wing (exophoria)	4.9 (1.2)	6.3 (1.4)	8.9 (1.3)[a]	5.3 (1.2)	6.9 (1.5)
DSST (total symbols drawn)[c]	46.3 (2.2)	44.1 (2.4)	42.3 (2.7)[a]	45.6 (2.4)	43.6 (2.4)
Physiological effects					
Pupil diameter (mm)[c]	5.8 (0.3)	4.3 (0.2)[a]	3.5 (0.2)[a]	4.5 (0.3)[a]	3.8 (0.2)[a]
Breaths per min[c]	12.4 (0.6)	10.9 (0.5)[a]	10.0 (0.4)[a]	11.4 (0.4)	10.4 (0.4)[a]

[a] $P<0.05$ compared with saline
[b] 1.3 HM rating significantly different from 10 MOR rating
[c] Trough rating

saline. Significantly higher peak PCAG scores were obtained with 1.3 mg hydromorphone and 10 mg morphine than with the saline condition, but the scores between the two active drug conditions did not differ significantly from each other. Trough BG scores and peak LSD scores in the 1.3 mg hydromorphone condition were significantly different than in the saline condition. Scores on the AMP scale were significantly higher in the 10 mg morphine condition than in the saline condition.

Adjective checklist

Hydromorphone. Significant dose-related increases were obtained on three adjectives from the opiate adjective checklist: "dry mouth" (Dose: $P<0.05$), "flushing" (Dose×Time: $P<0.01$), and "nodding" (Dose×Time: $P<0.001$). Ratings of "nodding" were still significantly elevated, relative to saline, at 300 min post-injection with the 1.3 mg dose of hydromorphone.

Peak effects. Table 1 illustrates the mean peak effects of opiate adjective checklist ratings that were sensitive to hydromorphone, (0.65, 1.3 mg) and morphine (5, 10 mg). Both the 1.3 mg dose of hydromorphone and the 10 mg dose of morphine significantly increased the mean peak rating of "nodding", relative to the saline condition, but did not significantly differ from each other. Only the 10 mg dose of morphine significantly increased mean peak ratings of "flushing" and "numb" relative to saline.

VAS

Hydromorphone. Significant Dose×Time effects (except where otherwise noted) were obtained on ratings of "coasting ('spaced out')" ($P<0.001$) (Fig. 1, middle frame), "confused" (Dose: $P<0.05$), "difficulty concentrating" ($P<0.001$), "dizzy" ($P<0.005$), "drunk" ($P<0.05$), "feel bad" (Dose: $P<0.005$), "floating" ($P<0.001$), "having pleasant bodily sensations" ($P<0.01$), "having unpleasant bodily sensations" (Dose: $P<0.001$), "heavy or sluggish feeling" ($P<0.001$), "high ('drug' high)" ($P<0.001$), "hungry" (Dose: $P<0.001$), "lightheaded" ($P<0.001$), "nauseous" (Dose: $P<0.01$), "sedated" (Dose: $P<0.001$), "sleepy (drowsy, tired)" ($P<0.005$), and "tingling" ($P<0.05$). All of these ratings, except "hungry", increased after drug administration. Effects were dose-related with all ratings. Average ratings of "coasting ('spaced out')", "difficulty concentrating", "heavy or sluggish feeling", and "sleepy (drowsy, tired)" peaked around 60–90 min after injection; all other ratings peaked at 5 or 15 min post-injection. For most ratings, duration of drug effect was 180–210 min.

Peak and trough effects. Table 1 presents mean peak and trough effects of VAS ratings that were sensitive to hydromorphone (0.65, 1.3 mg) and morphine (5,10 mg). For both drugs at one or more doses, peak ratings of "coasting ('spaced out')", "difficulty concentrating", "dizzy", "floating", "heavy or sluggish feeling", "high ('drug' high)", "lightheaded", "sedated", and "tingling" were increased relative to saline. Significantly higher ratings were generated by 1.3 mg hydromorphone compared to 10 mg morphine on the ratings of "coasting ('spaced out')", and "heavy or sluggish feeling." A number of other VAS adjectives which were significantly affected by both 1.3 mg hydromorphone and 10 mg morphine showed higher ratings with hydromorphone than with morphine, although the differences were not statistically significant (e.g., "high", "floating", "lightheaded"). Hydromorphone alone increased peak ratings of "confused" (1.3 mg dose), "drunk" (1.3 mg dose), "feel bad" (1.3 mg dose), "having pleasant bodily sensations" (1.3 mg dose), "nauseous" (1.3 mg dose), "sleepy (drowsy, tired)" (1.3 mg dose), and "having unpleasant bodily sensations" (both doses).

DEL questionnaire

Hydromorphone. Ratings of intensity of drug effect (Fig. 1, bottom frame) and drug liking were significantly increased in a dose-related manner (Dose×Time: $P<0.001$ and Dose×Time: $P<0.05$, respectively). Average ratings of both peaked at 5 min after drug injection, with duration of effect lasting up to 300 min for the intensity of drug effect rating and up to 15 min for the drug liking rating.

Peak and trough effects. Table 1 presents mean peak ratings from the DEL questionnaire that were sensitive to hydromorphone (0.65, 1.3 mg) and/or morphine (5, 10 mg). All four doses (0.65, 1.3 mg hydromorphone; 5, 10 mg morphine) significantly increased peak "feel drug effect" ratings, relative to the saline condition. The 0.65 mg dose of hydromorphone did not significantly differ from the 5 mg dose of morphine, nor did the 1.3 mg dose of hydromorphone differ from the 10 mg dose of morphine. Because of the bipolar nature of the drug liking question (i.e., 50=neutral and 0 and 100 are representative of extreme dislike and extreme liking, respectively), both peak and trough effect analyses were performed on this measure. Peak liking ratings were significantly higher than saline in all four active drug conditions, but not significantly different from each other. Trough liking ratings from the four active drug conditions did not differ significantly from those observed with saline.

Post-session adjective checklist

Hydromorphone. The only rating of the 17 ratings on this checklist that was affected by hydromorphone was "feel bad" ($P<0.05$). Post hoc testing revealed that the 1.3 mg dose of hydromorphone generated significantly higher ratings than saline.

Hydromorphone versus morphine. Significant Drug effects were obtained on the "feel bad" rating ($P<0.05$), with only the higher dose of hydromorphone generating significantly higher ratings than saline.

Psychomotor performance

Hydromorphone

Statistically significant effects were observed for the Maddox-Wing test (Dose×Time: $P<0.05$) and DSST (number completed, Dose: $P<0.005$; number correct, Dose: $P<0.01$). Hydromorphone (1.3 mg) produced exophoria, which was at its peak 15 min post-injection and persisted for up to 180 min after drug administration. Impairment on the DSST was limited to the 1.3 mg dose and was modest: mean number of symbols correctly drawn in the saline and 1.3 mg hydromorphone conditions (averaged across all time points) were 49.9 (0.8) and 47.2 (1.0), respectively.

Peak and trough effects

The highest dose of hydromorphone (1.3 mg) induced a greater degree of exophoria on the Maddox-Wing test than did saline ($P<0.001$; Table 1). This dose also produced significantly lower trough effects on the DSST (number completed, $P<0.05$; Table 1), when compared to

the saline condition. Peak and trough effects of morphine were not significantly different from saline on any psychomotor measure.

Physiological effects

Hydromorphone

Significant Dose×Time effects were obtained on both miosis ($P<0.001$) and respiration rate ($P<0.005$). Miotic effects were dose-related and persisted for the entire session with the two higher doses. Post hoc tests revealed that the 1.3 mg dose of hydromorphone decreased respiration rate at the 120 and 180 min post-injection time points.

Peak and trough effects

Trough miosis values were significantly lower in the hydromorphone (0.65 and 1.3 mg) and morphine (5 and 10 mg) conditions than in the saline condition (Table 1). Post hoc testing revealed no significant differences between hydromorphone and morphine when comparing either the two low or two higher doses. Trough respiration rates were significantly lower in the 0.65 and 1.3 mg hydromorphone conditions and in the 10 mg morphine condition, relative to saline (Table 1).

Relative potency analysis

Thirteen of the 30 measures summarized in Table 1 yielded dose-response functions that were significant ($P<0.01$), and did not differ from parallelism or show preparation differences ($P>0.05$), satisfying the criteria for a valid bioassay. Table 2 presents the relative potency estimates (hydromorphone to morphine) for the 13 measures. Bioassays revealed a geometric mean relative potency estimate of 0.097 (potency ratio of 10.3:1). This potency estimate indicates that 1.0 mg hydromorphone produces a similar magnitude of effect to that of 10 mg morphine.

Table 2 Results of hydromorphone/morphine bioassays

Dependent measure	Relative potency[a]	95% CL
PCAG (ARCI)	0.101	0.051–0.152
Flushing (Adjective checklist)	0.130	0.073–0.233
Difficulty concentrating (VAS)	0.110	0.061–0.169
Dizzy (VAS)	0.090	0.039–0.136
Floating (VAS)	0.105	0.068–0.145
High (VAS)	0.098	0.062–0.134
Lightheaded (VAS)	0.098	0.047–0.149
Sedated (VAS)	0.117	0.085–0.155
Maddox-Wing	0.080	0.036–0.118
DSST (number completed)	0.078	0.020–0.124
DSST (number correct)	0.074	0.016–0.121
Pupil diameter	0.106	0.090–0.122
Respiration rate	0.094	0.064–0.123
Geometric mean	0.097	

[a] Expressed as mg IV hydromorphone equivalent to 1 mg IV morphine

Discussion

The primary purpose of the present study was to characterize the subjective, psychomotor, and physiological effects of single doses of hydromorphone across a range of clinically-relevant doses. Hydromorphone is an opioid analgesic that is commonly used for relief for post-operative pain. Patients in clinical studies have reported effects of the drug including dizziness, sedation, nausea, vomiting, and pruritus. All of these effects, with the exception of pruritis, were reported in the present study. In the present study, subjective effects included effects that could be considered both positive and negative in nature. For example, subjects reported increased ratings of "having pleasant bodily sensations" and drug liking, but also reported increased ratings of "feel bad", "heavy or sluggish feeling", and "having unpleasant bodily sensations." This "mixed" profile has also been obtained with other opioids in our laboratory, including both full mu (morphine) and mixed-action opioid agonists [buprenorphine, nalbuphine, butorphanol, pentazocine] (Zacny et al. 1994a, 1994b, 1997a, 1997b, 1998). Hydromorphone at the highest dose tested impaired performance on the DSST, but did not affect reaction time, eye-hand coordination, logical reasoning, or memory processes. The degree of impairment by hydromorphone was relatively mild compared to impairment that we have observed with clinically relevant doses of benzodiazepines and other sedative drugs. For example, maximal impairment on the DSST from the highest dose of hydromorphone was about four fewer symbols drawn relative to baseline; typically in our sedative drug studies, maximal impairment is about 15–20 fewer symbols drawn relative to baseline (Thapar et al. 1995; Young et al. 1997). Miosis and respiration rate decreases were induced by hydromorphone, and the effects were dose-related.

Our results can be compared with studies that have assessed the effects of hydromorphone in opioid abusers because of the similarity in methodologies used (e.g., ARCI). In opioid abusers, hydromorphone (1.5–6.0 mg SC and IM) rather consistently increased ARCI MBG scores, drug liking ratings, and Good Effects visual analog ratings (Jasinski et al. 1977; Bickel et al. 1989; Preston et al. 1989, 1992; Preston and Bigelow 1994). In the present study, MBG scores were not increased by hydromorphone. However, our subjects did report "having pleasant bodily sensations" for up to 45 min after administration of 1.3 mg hydromorphone, and liking the drug's effects for up to 15 min after its administration. Unlike studies in which opioid abusers were tested, PCAG scores and ratings of "sleepy" and "drunk" were increased by hydromorphone in the present study. In addi-

tion, opioid abusers have not reported dysphoric effects from hydromorphone, while in the present study several measures indicative of dysphoria (e.g., elevated LSD scores, elevated ratings of "feel bad" and "having unpleasant bodily sensations") were obtained. Finally, psychomotor impairment from hydromorphone has not been found in opioid-abusing volunteers at the doses and particular performance measures assessed, but mild impairment was found in this study with non-drug-abusing volunteers. There appear, then, to be differences in how opioid abusers and non-drug abusers react to hydromorphone. Whether this is due to drug history or other factors (e.g., organismic) remains to be determined.

A secondary purpose of this study was to determine the relative potency of hydromorphone to that of the benchmark full mu opioid agonist, morphine. The relative potency estimate obtained in our study would suggest that 1.3 mg hydromorphone might produce greater effects than 10 mg morphine. That is, a relative potency of 10.3 would predict that 1.3 mg hydromorphone is equipotent to 13.4 mg morphine. Indeed, there was some evidence in this study of greater effects of 1.3 mg hydromorphone relative to 10 mg morphine. The VAS ratings of "coasting" and "heavy or sluggish feeling" were both increased by the two drugs, but the 1.3 mg dose of hydromorphone produced a significantly greater peak effect than did 10 mg morphine. Other mood ratings such as "high" and "lightheaded" showed a similar pattern (1.3 mg hydromorphone showing a greater effect than 10 mg morphine), but the differences did not achieve statistical significance. In addition, 1.3 mg hydromorphone increased several VAS ratings which were not affected by 10 mg morphine, including "confused", "drunk", and "sleepy (drowsy, tired)". Hydromorphone impaired some aspects of psychomotor performance, but morphine did not. It is also interesting to note that we obtained similar results in our cumulative dosing study when comparing hydromorphone and morphine and using a relative potency of 7.7 in choosing the cumulative doses; there were a number of instances in which the subjective effects of hydromorphone exceeded that of morphine (Walker and Zacny 1999). It is conceivable that had higher doses of morphine been tested in the present study as well as in the Walker and Zacny (1999) study (using a relative potency estimate of 10.3), the two drugs would have a near-comparable profile of subjective and psychomotor effects.

Several clinical studies have calculated relative potency ratios of parenteral hydromorphine to parenteral morphine, using analgesia as an endpoint. Relative analgesic potencies have varied across these studies (cf. Dunbar et al. 1996) and have been reported to be as low as 3 (Dunbar et al. 1996) and as high as 8.6 (Mahler and Forrest 1975). The most recent edition (9th) of *Goodman and Gilmans's The Pharmacological Basis of Therapeutics* (Hardman et al. 1996) lists 1.3 mg hydromorphone as being equipotent to 10 mg morphine, a relative potency of 7.7. The mean potency estimate calculated in our study using subjective, psychomotor, and physiological effects was 10.3. The mean potency estimate calculated in the only other known study which used subjective and miotic effects of subcutaneous hydromorphone and morphine was similar to ours, 9.4, and this was done in opioid abusers (Jasinski et al. 1977). We suggest that the relative potencies of hydromorphone to morphine on non-analgesic endpoints are slightly higher than the analgesic relative potencies (e.g., Mahler and Forrest 1975, Hardman et al. 1996) between the two drugs. This supposition could be tested empirically by including non-analgesic (subjective effects) as well as analgesic endpoints in clinical studies comparing the two opioids.

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