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Characterizing the Subjective, Observer-rated, and Physiological Effects of Hydromorphone Relative to Heroin in a Human Laboratory Study

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Abstract

Background—This study compared the effects of the several doses of the opioid agonists heroin and hydromorphone across two routes of administration in humans. The goal was to guide development of human laboratory studies of opioid effects and inform subsequent injection pharmacotherapy trials of hydromorphone-assisted treatment.

Methods—A within-subject (N=16), double-blind, double-dummy, placebo-controlled, evaluation of acute doses of heroin and hydromorphone was completed at four dose levels (placebo, low, medium, high) across two routes of administration (intravenous, subcutaneous) in non-physically dependent, opioid-experienced individuals. Subject and observer ratings, as well as physiological outcomes, were assessed.

Results—Within each route of administration, heroin and hydromorphone produced effects that were qualitatively similar on most variables across the doses examined. All effects were dose-dependent. The drugs produced different effects on VAS ratings of “Feels Like Heroin”, a Heroin Identification Test, observer agonist ratings, and oxygen saturation levels. Drug-dependent differences emerged at the highest doses in all cases. Few significant main effects of Route were identified and their pattern was not uniform. Relative potency calculations across all subject, observer, and physiological outcomes that met analysis criteria revealed similar profiles and resulted in mean heroin:hydromorphone potencies of 3.35:1 and 2.88:1 for the intravenous and subcutaneous routes, respectively, and intravenous:subcutaneous potencies of 0.47:1 and 0.49:1 for heroin and hydromorphone, respectively.

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Conclusions—Hydromorphone produced similar subjective and physiological effects as heroin, but was more potent than heroin. The current findings support the use of hydromorphone as a model for heroin in human laboratory and clinical treatment studies, and help identify appropriate hydromorphone dose conversion ratios to produce effects qualitatively similar to heroin.

Keywords

opioid; heroin; hydromorphone; potency; heroin-assisted treatment

Introduction

In 2015, 13.3 million people in the US reported having abused a prescription opioid or heroin, 2.6 million were estimated to have opioid use disorder (OUD), and 1.5 million people had sought treatment for OUD (Substance Abuse and Mental Health Services Administration (SAMHSA), Center for Behavioral Health Statistics and Quality. 2016). OUD costs US society an estimated \$8 billion annually in emergency room visits, criminal justice, and health problems (Strassels. 2009; Birnbaum et al. 2011). It is also contributing to unprecedented levels of opioid-related overdose deaths (Centers for Disease Control and Prevention (CDC). 2013; Rudd et al. 2014; Compton et al. 2016), and has resulted in increased HIV and Hepatitis C seroconversion rates among users (Bruneau et al. 2012; Havens et al. 2013). This study compared the effects of the opioid agonists hydromorphone and heroin at four dose levels via intravenous and subcutaneous routes of administration in humans. The goal was to guide development of human laboratory studies of opioid effects and inform subsequent injection pharmacotherapy trials of hydromorphone-assisted treatment, in an effort to help combat the opioid epidemic.

Hydromorphone was selected as a comparator to heroin because both drugs are potent mu opioid receptor agonists with relatively short durations of action (Parab et al. 1988; Chen et al. 1991; Rook et al. 2006), which suggests they may produce similar subjective effects. Hydromorphone has several additional characteristics that give it a practical advantage over other opioids for use in laboratory and therapeutic applications. It is available in the US legally as a Schedule II medication, is less stigmatized than heroin, and can be easily differentiated from other opioids in urine samples. Finally, P450 enzymes do not metabolize hydromorphone (Overholser and Foster. 2011; Zahari and Ismail. 2014), which differentiates it from other short-acting opioids such as morphine and oxycodone; this suggests that serum drug levels of hydromorphone may be more uniform across people relative to other opioids.

Numerous laboratory studies have used hydromorphone as a prototypical opioid comparator. Several studies conducted to support the development of buprenorphine/naloxone (Suboxone) for the treatment of OUD utilized acute hydromorphone challenges to assess buprenorphine's ability to block exogenous opioid use or relapse (Bickel et al. 1988a; Walsh et al. 1994; Walsh et al. 1995; Strain et al. 2000; Stoller et al. 2001; Sigmon et al. 2004). Additional studies administered hydromorphone to assess the degree to which novel medications produce subjective effects similar to abused opioids like heroin (Preston and Bigelow. 1994; Carroll et al. 2006; Duke et al. 2010; Duke et al. 2011) and evaluate opioid-related hyperalgesia in humans (Compton et al. 2000; Compton et al. 2003).

Hydromorphone has also been used as a standard against which the relative abuse potential of other opioid medications has been assessed (Walsh et al. 2008).

Hydromorphone is also being examined as a potential OUD therapeutic medication, which is an extension of research evaluating heroin (diacetylmorphine) maintenance for OUD treatment. Several randomized controlled heroin-assisted treatment trials have reported positive outcomes on retention in treatment (Haasen et al. 2007; Oviedo-Joekes et al. 2009), ongoing drug use (Perneger et al. 1998; Haasen et al. 2007; Demaret et al. 2015), heroin (Blanken et al. 2012), and quality of life (Haasen et al. 2007; Karow et al. 2010) when patients who are doing poorly in maintenance treatment with the long-acting opioid methadone are transitioned to heroin maintenance. Despite the positive results following heroin maintenance treatment (Ferri et al. 2011), this approach remains controversial and illegal in many countries. It is also a time-consuming, technical, and expensive process to differentiate illicit from prescribed use of heroin in urine samples, which is necessary to determine treatment efficacy (Paterson et al. 2005; Paterson and Cordero. 2006). The putative pharmacological similarities between heroin and hydromorphone have led to hydromorphone being evaluated as an alternative to heroin maintenance. A pilot study that randomized treatment-resistant methadone patients to maintenance on heroin (N=115) or hydromorphone (N=25) reported similar improvements in retention and illicit opioid use for both groups at the end of 12-months, with no medication-based differences in adverse event profiles (Oviedo-Joekes et al. 2010). A subsequent randomized, double-blind trial that assigned patients to maintenance on heroin (N=102) or hydromorphone (N=100) for a 6-month period also reported equivalent retention and illicit drug outcomes for the two groups (Oviedo-Joekes et al. 2016).

The use of hydromorphone to model heroin in human laboratory settings and as a potential alternative to heroin maintenance is based upon perceived similarities between the two drugs. However, at the time of this study, the efficacy and relative potency of the two drugs in the same subjects had not been empirically examined. This study was conducted, in part, to guide the development of the aforementioned hydromorphone-assisted treatment trials. Data were collected using a double-blind, double-dummy, placebo-controlled, within-subject, crossover, human laboratory model. Subjects received acute doses of hydromorphone and heroin at four different dose levels (coded here as placebo, low, medium, high dose) and through two routes of administration (intravenous [IV] vs. subcutaneous [SC]). Primary study outcomes were subject and observer-rated measures and physiological endpoints. A secondary analysis calculated the relative potency of hydromorphone when compared to heroin.

Methods

Subjects

Eighteen opioid-experienced users were recruited from 2000 – 2001 through local newspapers and by word of mouth. Eligible applicants had to report monthly intravenous use of opioids over the past 6 months and provide an opioid-positive urine sample during the screening period, but have no evidence of physical dependence on opioids during a 48-hour residential observation period. Exclusion criteria included evidence of physical dependence

on opioids or substances other than tobacco; history of seizures, cardiovascular disease, liver disease, or diabetes; taking prescription medications; abnormal blood chemistry, hematology, medical urinalysis, or electrocardiogram (ECG) results at screening; or presence of other significant medical and/or psychiatric disorders determined through clinical interviews. The study was conducted at the Center for Addiction and Mental Health (CAMH), a teaching hospital fully affiliated with the University of Toronto, and the Behavioral Pharmacology Research Unit (BPRU) at Johns Hopkins University. Both sites received IRB approval for the study and subjects provided voluntary informed consent to participate. Of the eighteen subjects enrolled, two were discharged prematurely for violating study procedures. Those subjects' data were not included in the analyses, resulting in a final sample size of N=16 (N=8 per site).

Study Procedures

Eligible subjects were admitted to a closed residential research unit for approximately 6-weeks.

Training Sessions—Two training sessions were conducted to familiarize subjects with study tasks prior to beginning sessions. Subjects were connected to a vital signs monitor and received IV injections of an intermediate dose of heroin (5mg) or hydromorphone (1.25mg) in randomized order across the sessions. Subjects also received a subcutaneous placebo injection, delivered concurrent with the IV injection, to model primary session procedures. A physician reviewed vital signs results to determine whether subjects could safely begin experimental sessions and no subjects were excluded at this stage.

Experimental Sessions—Subjects completed 16 experimental sessions in a residential human laboratory setting. Sessions were scheduled at least 48 hours apart to minimize carry-over effects and potential for acute opioid tolerance to influence results (Bickel et al. 1988b; Heishman et al. 1989; Heishman et al. 1990; Kirby et al. 1990). Subjects arrived in the laboratory at 08:00 and provided urine samples that were tested for evidence of recent drug use before consuming a calorie-controlled breakfast. Subjects who were cigarette smokers were allowed to smoke one cigarette before the session and another cigarette two hours after drug administration. Subjects were seated in a comfortable chair, had an intravenous catheter inserted, and were attached to a vital signs monitor that included ECG leads. Subjects completed baseline ratings (see Study Measures) 20 to 40 minutes prior to concurrent IV and SC injections of heroin or hydromorphone (see Study Drugs). Injections were a combination of placebo and active drug, with only one active drug being administered per session. A crash-cart with oxygen, a defibrillator, and the opioid antagonist naloxone was available onsite for emergencies. Study measures were collected at regular intervals throughout the 3-hour session. Specifically, data collection time-points were once per minute for the first 15 minutes, 16-, 30-, 60-, 90-, 120-, 150-, and 180-minutes post-drug administration (see Study Measures for specific collection schedules). Subjects were compensated up to \$1,040 for participation and performance on tasks.

Study Measures

Subject-reported Outcomes

Visual Analog Scale (VAS): Self-reported VAS ratings were collected at each post-drug time point and included “Drug Effect”, “High”, “Good Effect”, “Drug Liking”, “Rush”, and “Feels Like Heroin”. The primary VAS outcome was the numerical rating on a scale of 0 (not at all) to 100 (extremely).

Agonist Rating Scale: Subjects rated the severity of 16 opioid agonist symptoms on a scale of 0 (not at all) to 4 (extremely). Ratings were collected at baseline, 16-, 30-, 60-, 90-, 120-, 150-, and 180-minute time points, and the primary outcome was the summed value of ratings (range 0-64).

Drug vs. Money: A computer-based delivery of the Multiple Choice Procedure (Griffiths et al. 1993; Carter and Griffiths. 2009) was used to assess the relative abuse liability of the study drugs. This task was administered at the 30- and 150-minute time points. Subjects moved a computer cursor along a dollar-value continuum to indicate the point at which they would choose hypothetical money (ranging \$0-\$50) over that session’s drug. The primary outcome was the lowest dollar value at which the subject selected money over the drug, which was interpreted as the monetary value the subject assigned the drug.

Heroin Identification Test: Subjects were asked at the 16- and 60-minute time points to state whether the study drug they had received that day was heroin. To promote accurate discrimination, subjects earned \$8 for answering correctly, \$2 for responding “I can’t tell,” and \$0 for providing the wrong response. The primary outcome was the number of times per session the subject responded “Yes” (range 0-2).

Observer-rated Effects—A staff member observer rated the severity of subject agonist effects (nodding, itchy skin [scratching], talkative, and friendly) on a scale of 0 (not at all) to 4 (extremely) at baseline, 16-, 30-, 60-, 90-, 120-, 150-, and 180-minute time points. The primary outcome was the summed value of ratings (range 0-16).

Physiological Endpoints—Pupil diameter and blood oxygen saturation levels (assessed through pulse oximetry) were collected as measures of physiological response to study drugs at baseline, 16-, 30-, 60-, 90-, 120-, 150-, and 180-minutes. Pupil diameter was collected under consistent lighting using a customized pupillometry device (CAMH) or a Polaroid camera system (BPRU). Additional physiological data were also collected at the CAMH site only so are not included in the analyses.

Study Drugs

Subjects received IV and SC injections of acute doses of placebo, low, medium, and high quantities of heroin or hydromorphone during each study session. SC was used as a comparator to IV for several reasons. First, human laboratory studies frequently use non-intravenous routes for practical and safety reasons. Second, it was anticipated that heroin and/or hydromorphone maintenance trials would need to allow patients who had poor venous access to administer medications SC. Finally, SC was perceived as being potentially

more socially acceptable than IV from a public-relations standpoint, making it a useful comparator.

The order of drug administration was counter-balanced across subjects and the largest dose was never administered first. A 4:1 ratio of heroin to hydromorphone guided selection of the study doses, based upon research suggesting heroin was less potent than hydromorphone (Wallenstein et al. 1990; Reisine and Pasternak. 1996). SC doses were selected to be twice as large as IV doses. Thus, heroin was administered IV at 0mg, 2.5mg, 5mg, and 10mg and SC at 0mg, 5mg, 10mg, and 20mg. Hydromorphone was administered IV at 0mg, 0.63mg, 1.25mg, and 2.5mg and SC at 0mg, 1.25mg, 2.5mg, and 5mg. To maintain blinding, all IV doses were administered slowly over 30 seconds through a 23-gauge butterfly cannula and in an identical volume of fluid (2 ml), followed by a sterile saline flush of the cannula line (2ml). SC doses were injected into the upper arm. Hydromorphone was obtained from commercial sources and heroin was obtained commercially from international pharmaceutical suppliers. All study drugs were prepared independently at both sites by research pharmacists.

Data Analysis

The study hypothesized that hydromorphone would produce effects that were qualitatively similar to heroin within each route of administration. Subject demographics are summarized descriptively. Analyses first compared the peak/nadir (depending on the variable) change from baseline value for each primary outcome variable, derived by subtracting each variable's baseline (pre-drug) rating from the highest post-drug VAS, Agonist, and Observer Agonist ratings, and from the lowest pupil diameter and oxygen saturation endpoints. Proc Mixed Analyses of Covariance (ANCOVA) were used to compare main effects of Dose (placebo, low, medium, high), Drug (heroin vs. hydromorphone), and Route of Administration (IV vs. SC), as well as potential interactions (only significant interactions are described below). Site was included in all analyses as a covariate.

Second, outcomes for which a significant main effect of Dose was observed were then evaluated to determine the relative potency of heroin to hydromorphone and of IV to SC. Potency analyses used the Finney method for assessing parallel assays, which determined whether the dose effect relationship varied in terms of linearity or parallelism and whether slopes differed significantly from zero (Finney. 1964). Analyses were conducted using SPSS version 21 (IBM, Armonk, NY) or SAS 9.3 for Windows (SAS Institute, Cary NC) and alpha was set at $p = 0.05$.

Results

Subjects

Subjects were Caucasian (50%) and African American (50%), male (100%), and a mean (SD) of 37 (6.2) years old. They had a mean education of 12.4 (2.2) years, weighed 172.1 (25.3) pounds (78.2 [11.5] kg), reported using heroin for approximately 6.5 (6.1) years, and using heroin an average of 5.8 (4.5) days in the past 30.

Main Effects and Interactions

As expected, the general pattern of observed effects for both drugs and routes of administration was typical of those reported for opioid mu-agonists. Both drugs produced euphoric subject-reported effects, observable agonist effects, pupillary constriction, and decreases in oxygen saturation. Onset was slower via the SC versus IV route. All observed effects were dose-dependent, as measured by main effects of Dose (Table 1). Heroin and hydromorphone differentially increased some subjective, observer, and physiological indices, as measured by main effects of Drug. Several variables also demonstrated main effects of Route, though the pattern of those effects was inconsistent. Only two significant interactions were identified.

Significant main effects of Dose were observed for all 12 of the outcomes examined. Figure 1 illustrates the predominant pattern of dose-related profiles of effects across drugs and routes for three representative variables from all three categories: the Agonist Rating Scale (top panel), Observer Agonist Scale (middle panel), and Pupillary Diameter (bottom panel).

Significant main effects of Drug were only observed for 4 variables. These included the VAS “Feels Like Heroin” ($p=0.02$; Figure 2 top panel) and Heroin Identification Task ($p<0.01$; Figure 3 top panel), both of which required subjects to discriminate between heroin and hydromorphone. A significant Drug $\times$ Dose interaction ($F(3,222)=3.9$, $p=.01$) was also observed on the Heroin Identification Test, whereby subjects were more likely to accurately identify the drug as heroin as the dose increased (Figure 3, top panel). Oxygen saturation level also demonstrated a significant main effect of Drug ($p=0.03$) and a significant Drug $\times$ Dose interaction ($F(3,205)=3.4$, $p=.02$). Specifically, the highest dose of heroin significantly lowered oxygen saturation relative to hydromorphone, independent of route of administration (Figure 3, bottom panel). The final significant main effect of Drug was observed on the Observer Agonist Rating Scale ($p=0.04$; Figure 1, middle panel), suggesting that blinded observers’ ratings detected differences in subject response following heroin vs. hydromorphone administration.

Significant main effects of Route of Administration were observed on 5 variables. These data are provided in Table 1 and no consistent pattern regarding which route produced greater peak effects was observed. The most evident difference was that the IV route resulted in a more rapid escalation of effects relative to SC. The Figure 2 “Feels Like Heroin” VAS (top panel) and “Rush” VAS (bottom panel) graphs clearly illustrate the different speeds of onset between IV and SC routes in the first 15 minutes post injection.

Relative Potencies

Despite similarities in the general profile of effects, heroin and hydromorphone differed with regard to relative potency. Relative potency also differed across the two routes of administration. Table 2 presents relative potency estimates and corresponding 95% confidence intervals for all 12 outcomes evaluated. Comparison of potencies as a function of drug (heroin vs. hydromorphone) revealed 8 variables met the criteria for relative potency calculations within the IV route and that IV administration of the study drugs resulted in a total mean potency value of 3.35. These data suggest that IV heroin was less potent than IV

hydromorphone, with 3.35mg of heroin being equivalent to 1 mg of hydromorphone. Similarly, the drug comparison within the SC condition was valid for 10 variables and produced a mean potency of 2.88, indicating that 2.88mg of SC heroin was equivalent to 1 mg of SC hydromorphone. Similar calculations were performed to compare the two routes of administration and results suggested both heroin (mean=0.49) and hydromorphone (mean=0.47) were less potent when administered SC than when administered IV. The relative potencies for the VAS rating “Drug Effect” are presented for all drug and route of administration conditions in Figure 4 as an example.

Discussion

This was a within-subject, double-blind, double-dummy, placebo-controlled, cross-over, human laboratory study that compared four doses (placebo + three active doses) of heroin and hydromorphone across two different routes of administration (IV vs. SC) in experienced but non-physically dependent opioid users. These data were collected to support the use of hydromorphone as a model for heroin in human laboratory studies and to guide the development of hydromorphone-maintenance treatment trials. Hydromorphone produced effects qualitatively similar to heroin across a broad array of subject-reported, observer-rated, and physiological measures. Hydromorphone was more potent than heroin. Specifically, hydromorphone produced effects that were comparable to those produced by heroin doses that were approximately 3 times higher. Further, the similarity between the profile of effects produced by the SC and IV drug administration routes suggests that SC delivery of drug may be a valid alternative to IV, with appropriate conversions for relative potency differences. Overall, these results support the continued exploration of hydromorphone in both human laboratory and therapeutic settings.

Subjects in the current study significantly differentiated heroin from hydromorphone on the VAS “Feels Like Heroin” and the Heroin Identification Tasks. The basis upon which heroin was identified is unknown, but the fact that subjects were incentivized to correctly differentiate heroin from hydromorphone is likely an important factor. Subjects did not assign different monetary values to the two drugs on the Drug vs. Money Questionnaire, suggesting that the subjectively detected differences in drug effects were not of sufficient value to influence ratings of drug abuse liability. These results are in contrast to hydromorphone-maintenance trials, wherein patients who were randomized to heroin or hydromorphone maintenance were unable to accurately identify which medication they had received (Oviedo-Joekes et al. 2010; Oviedo-Joekes et al. 2016). The fact that subjects in those studies were physically-dependent, with higher tolerance levels than those in the current study, and were not rewarded for correct drug identification likely contributed to these differences.

The relative potency of heroin to hydromorphone identified in this study (3.35:1 for IV injection) is higher than the 2:1 ratio used to guide comparisons of therapeutic heroin and hydromorphone (Oviedo-Joekes et al. 2011). The fact that subjects in this study were not physically dependent on opioids and that hydromorphone was not being administered to treat opioid use disorder (for which outcomes related to suppression of withdrawal, cessation of cravings, and blockade of illicit opioid use would have been relevant) may explain this

difference. Although the similarities between heroin and hydromorphone observed in this study support the continued evaluation of hydromorphone as an alternative to heroin maintenance for OUD treatment, it is important to note the manner in which hydromorphone was administered in this study differs considerably from those treatment studies. Those studies administer significantly higher doses (e.g., over 200mg hydromorphone) for extended durations of time, in contrast to the smaller acute doses evaluated here. This distinction is important because the only between-drug differences observed in this study occurred at higher doses. Therefore, while the data from this study suggests that heroin and hydromorphone produce similar effects at the range of doses studied here, the results may not generalize to doses that are higher and administered chronically or to patients who are physically dependent on opioids.

This study was conducted in 2000 – 2001 to guide the development of human laboratory examinations of opioid effects and to support development of hydromorphone maintenance treatment trials. As a result, some data that were collected as part of the study are no longer available, including the detailed reporting of adverse events and subject substance use histories. It is also not possible for us to examine more thoroughly the differences observed in oxygen saturation levels at the highest doses, and no data exist to determine whether decreases in oxygen saturation resolved on their own, as a result of staff instruction to breathe, or from provision of supplemental oxygen. An additional limitation is that the enrolled sample was small, which is consistent with human laboratory studies of within-subject differences but could still limit generalizability. Further, though participation was open to women, only men chose to enroll in the study. Finally, subjects in this study were opioid-experienced but not physically dependent, so the degree to which their results may generalize to persons with opioid physical dependence are not known and warrants empirical investigation.

In summary, this study provides empirical evidence that acute doses of hydromorphone produce effects that are qualitatively similar to those produced by heroin across two different routes of administration and across subject-reported, observer-reported, and physiological outcomes. Hydromorphone was more potent than heroin for both IV and SC routes of administration. Results support the use of hydromorphone as a laboratory model of heroin and identify appropriate dose relationships for the continued exploration of hydromorphone maintenance for OUD treatment, particularly in settings for which heroin maintenance is prohibited or difficult.

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Figure 1.

Time course of Agonist Rating Scale (top panel), Observer Agonist Rating Scale (middle panel), and Pupil Diameter (bottom panel) for both intravenous (left) and subcutaneous (right) preparations at all times measured. Circles represent hydromorphone, squares represent heroin, dose values listed in legend. X-axis represents baseline (BL) and minutes post-dose, Y-axis represents mean peak (agonist rating scales) or nadir (pupil diameter) rating averaged across subjects.

Figure 2.

Time course of VAS rating "Feels Like Heroin" (Top Panel) and "Rush" (Bottom Panel) for both intravenous (left) and subcutaneous (right) preparations, at all times measured. Circles represent hydromorphone, squares represent heroin, dose values listed in legend. X-axis represents baseline (BL) and minutes post-dose, Y-axis represents mean peak rating averaged across subjects.

Figure 3.

Displays significant Drug (heroin, hydromorphone) $\times$ Dose (placebo, low, medium, high) interactions for the Heroin Identification Task (top panel; range 0-2) and Oxygen Saturation (bottom panel) as a function of mean peak (Heroin Identification Task) or nadir (oxygen saturation) ratings, collapsed across Route of Administration. Circles represent hydromorphone, squares represent heroin. Asterisks represent significance at $p < 0.05$, Y-axis represents mean, X-axis represents dose level (placebo, low, medium, high), and error bars present standard error of the mean.

Figure 4.

Mean peak VAS rating of "Drug Effect" for both intravenous (left) and subcutaneous (right) preparations, collapsed across time points. Circles represent hydromorphone, squares represent heroin. Y-axis represents mean peak rating, X-axis presents dose in mg and error bars present $\pm$ standard error of the mean. Relative potency (RP) values and 95% confidence intervals are shown.

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Table 1

Mean Peak or Nadir Ratings

	Intravenous										Subcutaneous				Main Effects				Route of Administration			
	Heroin			Hydromorphone			Heroin				Hydromorphone		Drug		Dose							
	0mg	2.5mg	5.0mg	10.0mg	0mg	0.63mg	1.25mg	2.5mg	0mg	5.0mg	10.0mg	20.0mg	0mg	1.25mg	2.5mg	5.0mg	F (1,15)	p-value		F (3,45)	p-value	
Subject Reported Outcomes																						
Visual Analog Scales (range 0 - 100)																						
Drug Effect	5.9	21.6	41.7	46.8	1.3	21.1	37.4	44.5	1.1	21.3	32.1	47.3	1.9	19.1	23.9	45.3	1.83	0.20	76.30	<0.001	0.28	0.84
High	8.4	21.3	43.6	47.9	4.6	22.7	39.3	45.4	3.8	22.0	32.9	46.9	5.4	21.6	25.0	42.1	1.63	0.22	73.80	<0.001	4.30	0.06
Good Effect	8.5	23.7	45.3	49.2	4.6	25.1	41.7	47.6	3.9	24.9	36.1	49.4	4.9	24.6	28.3	43.1	1.47	0.24	69.24	<0.001	3.03	0.10
Drug Liking	6.2	21.6	33.7	39.4	5.4	15.3	27.6	32.3	6.6	21.4	29.5	34.5	7.8	23.3	16.9	30.9	3.14	0.10	24.89	<0.001	0.31	0.59
Rush	5.8	18.9	30.4	42.6	4.3	20.6	31.2	39.9	3.4	13.1	28.4	35.2	7.3	15.8	19.7	29.9	0.30	0.59	43.75	<0.001	6.16	0.03
Feels Like Heroin	6.0	26.2	48.6	44.4	4.1	24.4	37.3	34.3	6.1	27.5	41.8	58.4	6.6	24.5	28.4	42.4	6.44	0.02	38.52	<0.001	0.22	0.65
Agonist Rating Scale (0-64)	1.0	3.8	6.7	9.8	2.3	3.6	5.8	7.9	2.2	5.1	9.4	11.7	1.6	4.6	7.1	12.2	1.25	0.28	52.39	<0.001	9.72	<01
Drug vs. Money Questionnaire (0-50)	1.3	4.9	11.1	16.2	1.1	3.7	10.5	13.1	1.3	7.7	9.9	19.3	1.8	7.8	8.3	14.8	2.45	0.14	51.43	<0.001	1.74	0.21
Heroin Identification Task (0-2)	0.2	0.9	1.6	1.4	0.3	0.8	0.9	0.4	0.1	1.0	1.4	1.8	0.4	0.6	0.9	1.4	13.01	<01	23.20	<0.001	4.48	<01
Observer Agonist Rating Scale (0-16)	0.2	1.1	2.1	3.3	0.3	0.9	1.6	2.0	0.4	1.9	2.3	4.4	0.2	1.3	2.2	3.6	5.11	0.04	42.65	<0.001	8.85	<01
Physiological Endpoints																						
Pupil Diameter (mm) ^a	-0.7	-1.4	-2.3	-2.9	-0.9	-1.5	-2.0	-2.7	-0.8	-2.3	-2.8	-2.7	-0.6	-2.0	-2.4	-3.0	1.50	0.23	96.30	<0.001	8.64	0.01
Oxygen Saturation ^a	-1.6	-2.1	-2.3	-4.1	-1.4	-1.5	-2.1	-2.6	-1.6	-2.1	-1.8	-4.7	-1.6	-1.8	-2.4	-2.6	6.34	0.03	14.48	<0.001	0.21	0.65

All values represent mean peak change from baseline unless otherwise noted. Results based on Proc Mixed analysis and adjusted for site. mg=milligram, mm=millimeter

^aResults represent nadir ratings

Table 2

Relative Potencies

	Heroin:Hydromorphone				Intravenous:Subcutaneous			
	Intravenous		Subcutaneous		Heroin		Hydromorphone	
	Relative Potency	Confidence Interval	Relative Potency	Confidence Interval	Relative Potency	Confidence Interval	Relative Potency	Confidence Interval
Subject-reported Outcomes								
Visual Analog Scales								
Drug Effect	3.49	2.21–5.29	3.22	2.36–4.28	0.42	0.28–0.61	0.38	0.24–0.56
High	3.61	2.37–5.36	3.01	2.03–4.37	0.41	0.27–0.60	–	–
Good Effect	3.71	2.38–5.66	2.94	1.19–4.20	0.43	0.29–0.63	0.33	0.18–0.52
Drug Liking	2.37	0.88–4.31	2.12	0.12–5.24	0.38	0.13–0.78	0.43	0.10–1.28
Rush	3.98	2.49–6.36	3.00	1.64–4.85	0.37	0.23–0.55	–	–
Feels Like Heroin	–	–	2.17	0.73–3.97	0.59	0.34–1.10	0.49	0.17–1.36
Agonist Rating Scale	3.06	1.69–4.94	3.44	2.29–4.99	–	–	–	–
Drug vs. Money Questionnaire	3.19	1.77–5.24	2.96	1.86–4.36	–	–	0.61	0.35–1.20
Heroin Identification Task	–	–	–	–	0.62	0.22–2.93	–	–
Observer Agonist Rating Scale	–	–	2.94	1.70–4.56	–	–	–	–
Physiological Endpoints								
Pupil Diameter ^a	3.42	4.33–2.66	2.96	5.13–1.43	–	–	–	–
Oxygen Saturation ^a	–	–	–	–	0.51	1.40–0.20	0.67	143.36–0.13
Mean Relative Potency	3.35		2.88		0.47		0.49	

Relative potencies and confidence intervals are shown only for assays for which the regression was significant and no significant differences in preparation, linearity, or parallelism were observed. Assays were analyzed based upon maximum peak values unless otherwise noted. Relative potency is expressed as the mg of heroin necessary to produce the same effect of 1mg of hydromorphone, and as the mg of intravenous administration necessary to produce the same effect of 1mg of subcutaneous administration.

^a Analysis conducted on nadir values