

OPIOIDS & SUBSTANCE USE DISORDERS SECTION

Original Research Article

Evaluation of the Relative Intranasal Abuse Potential of a Hydrocodone Extended-Release Tablet Formulated with Abuse-Deterrence Technology in Nondependent, Recreational Opioid Users

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Abstract

Objective. To assess the intranasal abuse potential of hydrocodone extended-release (ER) tablets developed with CIMA Abuse-Deterrence Technology compared with hydrocodone powder and hydrocodone bitartrate ER capsules (Zohydro ER, original formulation [HYD-OF]).

Design. Single-dose, randomized, double-blind, quadruple-dummy, active- and placebo-controlled, crossover study.

Setting. One US site.

Subjects. Healthy, adult, nondependent, recreational opioid users.

Methods. Subjects able to tolerate intranasal hydrocodone and discriminate hydrocodone from placebo were eligible for study enrollment. Eligible participants randomly received intranasal hydrocodone ER, intranasal hydrocodone powder, intranasal HYD-OF,

intact oral hydrocodone ER, and placebo. Coprimary pharmacodynamic end points were a maximum effect on “at the moment” Drug Liking visual analog scale and Overall Drug Liking visual analog scale. Pharmacokinetics and safety were assessed.

Results. Mean maximum effect for “at the moment” Drug Liking was significantly ($P < 0.01$) lower for intranasal hydrocodone ER (72.8) compared with hydrocodone powder (80.2) and HYD-OF (83.2). Similar results were observed for Overall Drug Liking maximum effect (68.5 vs 77.1 and 79.8, respectively; $P < 0.01$). Secondary end points, including balance of effects and positive, sedative, and other effects, were consistent with these results. Intranasal treatments showed significantly greater effects vs placebo, while intact oral hydrocodone ER was similar to placebo. For each treatment, plasma concentration-time profiles paralleled “at the moment” Drug Liking over time. Incidences of adverse events for intranasal treatments were 52% for hydrocodone ER, 53% for hydrocodone powder, and 61% for HYD-OF.

Conclusions. The statistically significant differences between hydrocodone ER vs hydrocodone powder and HYD-OF for the primary drug liking end points indicate a lower intranasal abuse potential with hydrocodone ER in healthy, nondependent, recreational opioid users.

Key Words. Extended Release; Hydrocodone; Opioid Analgesics; Substance Abuse; Abuse Potential; Drug Liking

Introduction

Opioids are well established in the management of acute and cancer pain, and are also commonly used for chronic nonmalignant pain [1]. Over the past two decades, prescription opioid abuse, which is defined as intentional, nontherapeutic use to achieve a desired effect, has increased in conjunction with diversion of these medications through illegitimate channels primarily to nonpatients [2–4]. In an analysis of data from 2004 to 2011, the overall nonmedical use of opioids for psychic effect, dependence, or suicide attempt increased 165% compared with a 65% increase in medicinal uses of opioids [3]. As a result, numerous state and national government organizations have implemented various strategies to address this serious public health and safety concern [2,4].

Abuse of prescription opioid products is often achieved through manipulation, which typically involves crushing a pharmaceutical product and either swallowing, snorting, smoking, or dissolving it for injection [4]. The US Food and Drug Administration (FDA) endorses the development of abuse-deterrent features into prescription opioid formulations to make manipulation more difficult or make

abuse of the manipulated product less rewarding [4]. To evaluate these potential abuse-deterrent products, the FDA suggests three categories of studies: laboratory-based in vitro manipulation and extraction studies, pharmacokinetic studies, and clinical abuse potential studies [4]. Recent data suggest that abuse-deterrent products have been associated with a reduction in overdose and abuse of these formulations, but an increased rate of illicit drug use was also reported [2,5–7].

Hydrocodone bitartrate has been formulated into a single-agent ER tablet (hydrocodone ER [Vantrela ER]; Teva Pharmaceuticals, Inc., Frazer, PA, USA) to provide sustained pain relief with twice-daily dosing. Hydrocodone ER employs CIMA Abuse-Deterrence Technology (ADT; CIMA Labs, Inc., Brooklyn Park, MN, USA) that allows for controlled release of hydrocodone over an extended period and resists rapid release of hydrocodone when the tablets are comminuted (i.e., broken into small pieces by crushing, milling, grating, or grinding) [8]. The formulation has also been shown to provide protection against dose dumping when tablets are taken with alcohol [9]. The pharmacokinetics of this hydrocodone ER formulation has been characterized in several studies [9–12].

Epidemiologic studies suggest that oral ingestion of the intact product is the most common route of administration in the abuse of immediate-release (IR) hydrocodone products [13,14]. This results, in part, from the fact that hydrocodone was available only as an IR product until recently. In contrast, ER formulations of opioids are more likely to be manipulated and then swallowed, inhaled, or injected [13–15]. The abuse-deterrent properties of oral hydrocodone ER were characterized in a previous clinical abuse liability study in 49 nondependent recreational opioid users [16]. Oral administration of intact and finely crushed hydrocodone ER tablets was associated with significantly lower peak “at the moment” Drug Liking compared with oral hydrocodone active pharmaceutical ingredient powder, which was used as a surrogate for IR hydrocodone. In addition, peak “at the moment” Drug Liking after administration of intact hydrocodone ER was comparable with that of placebo.

The current study characterizes the abuse-deterrent properties associated with intranasal administration of finely milled hydrocodone ER, the second most common route of abuse [14]. The primary objective of this study was to assess the relative abuse potential of finely milled intranasal hydrocodone ER compared with intranasal hydrocodone powder; finely milled intranasal hydrocodone bitartrate ER capsules original formulation (HYD-OF; Zohydro ER, a registered trademark of Pernix Ireland Pain Limited, Morristown, NJ), a commercially available, non-abuse-deterrent formulation of hydrocodone ER available at the time the study was conducted (a reformulated version with BeadTek Technology was approved in January 2015, which also does not have abuse-deterrence labeling) [17]; and intact oral hydrocodone ER in healthy nondependent adults with a history of recreational and intranasal opioid use.

Methods

This single-dose, randomized, double-blind, quadruple-dummy, active- and placebo-controlled, crossover study was performed at one study site in the United States (PRA Health Sciences, Salt Lake City, UT, USA) from May through July 2014. This study design was consistent with the draft FDA guidance on clinical abuse potential studies of abuse-deterrent opioid formulations available at the time of the study and was conducted in a drug-experienced population who were prequalified based on their ability to distinguish active drug from placebo [18]. The study was conducted in accordance with the International Conference on Harmonisation Good Clinical Practice Consolidated Guideline [19] and applicable national and local laws and regulations. The study protocol was reviewed and approved by the institutional review board before study initiation, and all subjects provided written informed consent before any study-related procedures were performed.

Subjects

Men and women age 18 to 55 years were eligible for study enrollment if they had a body mass index of 18 through 32 kg/m² and were in good health as determined by medical and psychiatric history, medical examination, electrocardiogram (ECG), serum chemistry, hematology, urinalysis, and serology. Subjects were required to have a history of recreational opioid use to achieve a “high” at least 10 times in the last year and on at least one occasion within 12 weeks before screening but could not be physically dependent on opioids, as shown by successful completion of a naloxone challenge (i.e., no signs or symptoms of opioid withdrawal as assessed by a Clinical Opiate Withdrawal Scale score of <5 after administration of intravenous naloxone). Subjects who abused multiple drugs must have expressed a preference for opioids. In addition, subjects had to have experience with the intranasal use of opioids on at least three occasions in the year before screening.

Exclusion criteria included any clinically significant, uncontrolled medical condition or abnormalities in laboratory, ECG, vital sign, or physical examination findings, including oxygen saturation of less than 95% after resting for five minutes; pregnancy or lactation; history or current diagnosis of substance dependence or had participated in or was seeking treatment for substance-related disorders; current consumption, or habitual consumption within the past two years, of alcohol in a quantity of more than 28 units per week for men or more than 21 units per week for women; and inability to abstain from smoking for six hours during any day or abstain from caffeine intake for 20 hours during any day. Subjects were also excluded if they had any clinically important condition of the intranasal cavity, had a genotype associated with poor metabolism of cytochrome P450 2D6 substrates, had donated blood (>450 mL)

within 56 days prior to screening, or had known sensitivity or idiosyncratic reaction to study drugs, their related compounds, or naloxone.

Study Design

After subject evaluation in the screening period, eligible participants entered a randomized, double-blind, placebo-controlled, two-treatment, two-period crossover qualification phase to ensure they could tolerate a 45 mg intranasal dose of hydrocodone powder and discriminate between the effects of hydrocodone and placebo. Eligible subjects were randomly assigned in a 1:1 ratio to receive intranasal placebo powder and intranasal hydrocodone powder 45 mg with a minimum 48-hour washout between treatments.

For subjects to continue into the treatment phase, they had to tolerate the 45 mg dose of intranasal hydrocodone powder; have a greater response to intranasal hydrocodone powder than to intranasal placebo (≥ 15 -point difference in peak score) for “at the moment” Drug Liking and Overall Drug Liking visual analog scales (VAS; both 100-point bipolar drug-liking VAS [0 = strong disliking, 50 = neutral, 100 = strong liking]); and have an acceptable response to placebo (between 40 and 60, inclusive for “at the moment” Drug Liking and Overall Drug Liking VAS) and an acceptable response to hydrocodone powder on all measures.

After a minimum seven-day washout period, qualified subjects entered the randomized, double-blind, quadruple-dummy, placebo-controlled, five-period, crossover treatment phase of the study. Eligible subjects received, in random sequence, each of the following interventions separated by a minimum seven-day washout:

- intranasal finely milled hydrocodone ER 45 mg and one intact oral placebo tablet;
- intranasal hydrocodone 45 mg powder and one intact oral placebo tablet;
- intranasal finely milled HYD-OF 45 mg (commercially available hydrocodone bitartrate ER capsule formulation in May 2014 [prior to reformulation approval in January 2015]) and one intact oral placebo tablet;
- intact oral hydrocodone ER 45 mg and intranasal placebo;
- placebo (intranasal and oral).

Intranasal hydrocodone ER, HYD-OF, and placebo were comminuted using an Elite mixer. For each intervention, subjects insufflated the intranasal material using straws and ingested the oral tablet with approximately 240 mL of noncarbonated, room temperature water after an overnight fast of approximately eight hours. All subjects were asked to return for a follow-up visit approximately 48 to 72 hours after discharge from the study center following their final dose of study medication.

Pharmacodynamic Assessments

A summary of the questionnaires and pharmacodynamic measures used to evaluate subjective drug abuse potential is available in the Supplementary Data.

Copriary Measures

The copriary pharmacodynamic measures used to assess abuse potential were “at the moment” Drug Liking VAS (part of the Drug Liking and Effects Questionnaire [DLEQ]) and the Overall Drug Liking VAS score (drug liking over a full 24-hour period after study medication administration) using the parameter of peak score (maximum effect [E_{max}]). Each of these measures was scored using a bipolar VAS ranging from a strong negative response (score of 0) to a strong positive response (score of 100) with a neutral midpoint (score of 50).

Secondary Measures

Secondary pharmacodynamic measures for assessment of abuse potential included measures of balance of drug effects, positive drug effects, negative drug effects, sedative effects, and other drug effects based on the DLEQ, Take Drug Again Assessment (TDAA) score, Price Value Assessment Questionnaire (PVAQ) score, and subscales of the Addiction Research Center Inventory (ARCI) (Supplementary Data, Table S1). The Lysergic Acid Diethylamide (LSD) subscale of ARCI assesses subjective negative effects of drugs with statements such as “I feel drowsy” and “I feel anxious and upset.” Nasal effects were measured by Ease of Snorting VAS, with responses ranging from 0 = very easy to 100 = very difficult, and by E_{max} and area under the effect curve from 0 to 8 hours ($AUEC_{0-8h}$) of the Subject-Rated Assessment of Intranasal Irritation (SRALI) scales: Burning, Need to Blow Nose, Runny Nose/Nasal Discharge, Facial Pain/Pressure, and Nasal Congestion. The SRALI scales were rated on a six-point scale from 0 = not observed/no problem to 5 = very severe problem/“as bad as can be.” In addition, the physiologic effect of the treatments was assessed by the minimum effect (E_{min} ; minimum pupil diameter) and $AUEC$ for pupillometry. Pupil diameter measurements were completed prior to and over 48 hours after each administration of study medication.

Pharmacokinetic Measures

During the treatment phase, blood samples were collected within 60 minutes before study drug administration and at 0.25, 0.5, 0.75, 1.0, 1.25, 1.5, 2, 2.5, 3, 4, 6, 7, 8, 9, 10, 12, 24, 36, and 48 hours after study drug administration. Plasma concentrations of hydrocodone and its active metabolite, hydromorphone, were determined by Pharmaceutical Product Development (Richmond, VA, USA) using a validated high-performance

liquid chromatography method with tandem mass spectrometric detection. The validated quantifiable range of the assay was 0.100 to 100 ng/mL for hydrocodone and 0.0500 to 50.0 ng/mL for hydromorphone (bioanalytical methods same as previously described by Darwish et al. [20]).

The following pharmacokinetic parameters for hydrocodone and hydromorphone were calculated for each active treatment using noncompartmental methods (Pharsight Phoenix WinNonlin, version 6.3; Pharsight Corporation, Mountain View, CA, USA, 2011–2012): maximum plasma drug concentration (C_{max} ; by inspection), time to C_{max} (t_{max} ; by inspection), area under the plasma concentration-time curve (AUC) from time 0 to the time of the last measurable drug concentration (AUC_{0-t}), AUC from time 0 to infinity ($AUC_{0-\infty}$), apparent plasma terminal elimination rate constant (λ_z), elimination half-life ($t_{1/2}$), abuse quotient (AQ; calculated as C_{max}/t_{max}), and percent extrapolation (calculated as $100 \times [AUC_{0-\infty} - AUC_{0-t}]/AUC_{0-\infty}$). AUC and C_{max} ratios were calculated for comparisons of intranasal hydrocodone ER vs intact oral hydrocodone ER, intranasal hydrocodone powder vs intranasal HYD-OF, and intranasal HYD-OF vs intranasal hydrocodone powder.

To assess early exposure over relevant time periods, specifically to time of peak of each finely milled treatment and the IR surrogate in the context of exposure through peak for the ER tablet when used as intended, the following parameters were also assessed: AUC from time 0 to the median t_{max} for intranasal hydrocodone powder ($AUC_{0-t_{max, IN(powder)}}$), AUC from time 0 to the median t_{max} for hydrocodone ER when finely milled and given intranasally ($AUC_{0-t_{max, ER(IN)}}$), AUC from time 0 to the median t_{max} for hydrocodone ER given orally ($AUC_{0-t_{max, ER(oral)}}$), and AUC from time 0 to the median t_{max} for HYD-OF when given intranasally ($AUC_{0-t_{max, Zoh(IN)}}$).

Safety

Safety and tolerability were assessed by monitoring adverse events (AEs), clinical laboratory test results, ECG and physical examination findings, vital sign measurements (pulse, respiratory rate, seated blood pressure), oxyhemoglobin saturation (SpO_2) measurements, suicidality assessments, and concomitant medication use.

Statistical Analysis

A minimum of 30 evaluable subjects was required to complete the double-blind, crossover treatment phase to achieve 90% power to detect a difference of 12 to 20 points on a 100 mm VAS between a pair of treatments, based on a two-sided paired t test with a statistical significance of 0.05. The within-subject standard deviation was estimated based on a published intranasal abuse liability study with an abuse-deterrent formulation of oxycodone [5] as there were no intranasal abuse liability data for hydrocodone at the time of the study.

Pharmacodynamic parameters for each treatment were summarized using descriptive statistics. Continuous and ordinal categorical pharmacodynamic parameters were analyzed using a mixed-effects model that included study treatment, period, and treatment sequence as fixed effects, baseline (predose) measurement as a covariate where applicable, and subject nested within sequence as a random effect. The first-order carryover effect was included in the model as a fixed effect and was to be dropped if not statistically significant at the 25% significance level. Pharmacodynamic data that did not meet assumptions of normality were assessed using Friedman's test (overall treatment effect); pairwise treatment comparisons were assessed using the Wilcoxon sign-rank test on the within-subject differences. For the primary pharmacodynamic end points, the comparison between intranasal hydrocodone powder and placebo was assessed first to ensure validity of the study and end points. As the treatment differences were significant ($P < 0.001$ for both end points), the study was considered valid and further comparisons were made. A responder analysis for the percent reduction in E_{\max} was also conducted. The desired percent reduction in E_{\max} is unknown; therefore, responders were categorized into decile reductions in E_{\max} of 30% or greater, 40% or greater, and 50% or greater. Pharmacokinetic variables were summarized using descriptive statistics, including mean, standard deviation, geometric mean, median, minimum, and maximum. Mean percent differences (representing the mean of individual subject differences) in pharmacokinetic variables were calculated for pairwise treatment comparisons.

Results

Subjects

Of the 163 subjects screened, 73 were enrolled and randomized in the qualification phase and 45 were randomly assigned to a treatment sequence (Supplementary Data, Figure S1). All 45 subjects received at least one dose of study medication and were included in the safety analysis set. Thirty-four subjects received all five treatments and were included in the pharmacodynamic analysis set. Randomized subjects in the treatment phase were predominantly white (87%) and male (73%) and had a mean age of 27.8 years (range = 19.0–52.0 years) and a mean body mass index of 23.6 kg/m² (range = 18.4–30.4 kg/m²).

Coprimary Pharmacodynamic Measures

Mean E_{\max} for "at the moment" Drug Liking was significantly lower for intranasal hydrocodone ER (72.8, SD = 13.7) compared with intranasal hydrocodone powder (80.2, SD = 12.6; $P = 0.004$) and intranasal HYD-OF (83.2, SD = 11.9; $P < 0.001$) (Figure 1A). All three intranasal treatments were associated with significantly ($P < 0.001$) higher scores for "at the moment" Drug Liking compared with intact oral hydrocodone ER (57.3, SD = 11.0) and placebo (58.6, SD = 11.3), which had

similar scores. E_{\max} for Overall Drug Liking (over a full 24-hour period after study drug administration) was also significantly lower for intranasal hydrocodone ER (68.5, SD = 19.3) compared with intranasal hydrocodone powder (77.1, SD = 14.7; $P = 0.004$) and intranasal HYD-OF (79.8, SD = 15.9; $P < 0.001$) and significantly higher compared with intact oral hydrocodone ER (57.8, SD = 15.7; $P < 0.001$) and placebo (57.7, SD = 13.9; $P = 0.001$) (Figure 1B).

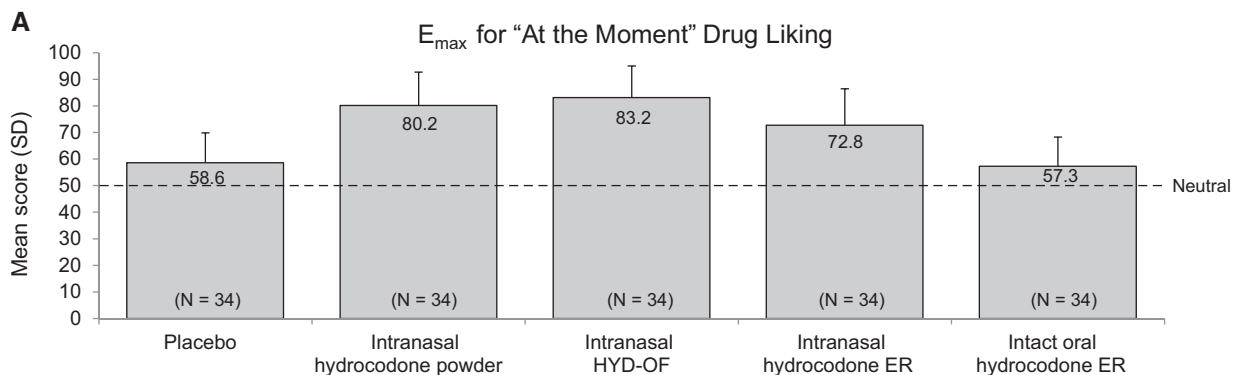
Mean "at the moment" Drug Liking over time for each treatment is presented in Figure 2A. Administration of intranasal hydrocodone powder and intranasal HYD-OF resulted in rapid increases in mean "at the moment" Drug Liking VAS scores, with high mean scores (>65) from 0.5 hours until at least 4 hours postdose. In contrast, intranasal hydrocodone ER was associated with a slower rise in Drug Liking VAS scores and a lower peak score. The mean score was greater than 65 for a shorter time period and later in the time course profile. Intact oral hydrocodone ER and placebo had comparable Drug Liking VAS scores over time, with little increase above neutral (50).

The proportions of subjects who showed some reduction in E_{\max} scores (ie, responders) by treatment for "at the moment" Drug Liking and Overall Drug Liking are shown in Figure 3. For "at the moment" Drug Liking, 35.3% of subjects showed 30% or greater reduction with intranasal hydrocodone ER compared with intranasal hydrocodone powder, while 17.6% showed 50% or greater reductions. Results for Overall Drug Liking were 34.4% and 31.3%, respectively. For the comparison of intranasal hydrocodone ER and intranasal HYD-OF, 30% or greater and 50% or greater reductions were 38.2% and 23.5% for "at the moment" Drug Liking and 48.5% and 30.3% for Overall Drug Liking.

Measures of Balance Effects

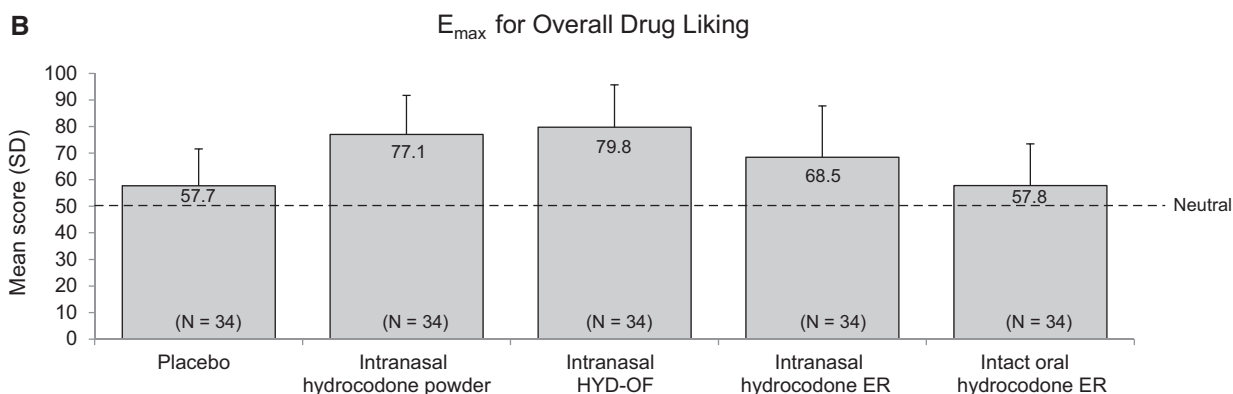
Outcomes for secondary pharmacodynamic measures (Table 1) were generally consistent with the coprimary pharmacodynamic results. Overall balance of effects included measures of maximum "disliking" ("at the moment" Drug Liking VAS E_{\min} and Overall Drug Liking VAS E_{\min}) and measures of overall effects, including TDAA VAS E_{\max} , PVAQ E_{\max} , and AUEC of "at the moment" Drug Liking. "At the moment" Drug Liking VAS E_{\min} scores were significantly lower with intranasal hydrocodone ER compared with intranasal hydrocodone powder (42.9 vs 46.8; $P = 0.0056$) and intranasal HYD-OF (42.9 vs 46.4; $P = 0.0181$), while the latter two treatments were not significantly different ($P = 0.8388$). The three active intranasal treatments did not show significantly different "at the moment" Drug Liking VAS E_{\min} scores compared with placebo, and intranasal hydrocodone ER was not significantly different from intact oral hydrocodone ER.

Results for Overall Drug Liking VAS E_{\min} were similar, with significantly ($P < 0.001$) lower scores after intranasal



Pairwise Comparisons: E_{max} for “At the Moment” Drug Liking

Comparisons of intranasal treatments	LS mean difference (95% CI)	P value
IN hydrocodone ER vs IN hydrocodone powder	-6.83 (-11.47 to -2.19)	0.004
IN hydrocodone ER vs IN HYD-OF	-9.92 (-14.52 to -5.32)	<0.001
IN HYD-OF vs IN hydrocodone powder	3.09 (-1.54 to 7.73)	0.189
Comparisons with placebo		
IN hydrocodone powder	19.34 (14.76 to 23.92)	<0.001
IN HYD-OF	22.43 (17.82 to 27.04)	<0.001
IN hydrocodone ER	12.51 (7.89 to 17.12)	<0.001
Comparison of intranasal and intact oral hydrocodone		
IN hydrocodone ER vs oral hydrocodone ER	15.39 (10.75 to 20.02)	<0.001



Pairwise Comparisons: E_{max} for Overall Drug Liking VAS Scores

Comparisons of intranasal treatments	LS mean difference (95% CI)	P value
IN hydrocodone ER vs IN hydrocodone powder	-8.02 (-13.50 to -2.55)	0.004
IN hydrocodone ER vs IN HYD-OF	-11.67 (-17.10 to -6.25)	<0.001
IN HYD-OF vs IN hydrocodone powder	3.65 (-1.82 to 9.12)	0.189
Comparisons with placebo		
IN hydrocodone powder	17.02 (11.62 to 22.42)	<0.001
IN HYD-OF	20.67 (15.22 to 26.11)	<0.001
IN hydrocodone ER	8.99 (3.55 to 14.43)	0.001
Comparison of intranasal and intact oral hydrocodone		
IN hydrocodone ER vs oral hydrocodone ER	9.52 (4.05 to 14.99)	<0.001

Figure 1 Coprimary end points: mean (SD) E_{max} scores for **(A)** “at the moment” Drug Liking and **(B)** Overall Drug Liking by treatment. 0 = strong disliking; 50 = neutral; 100 = strong liking. CI = confidence interval; E_{max} = maximum effect; ER = extended release; HYD-OF = non-abuse-deterrent hydrocodone ER–original formulation; IN = intranasal; LS = least squares; PO = oral; VAS = visual analog scale.

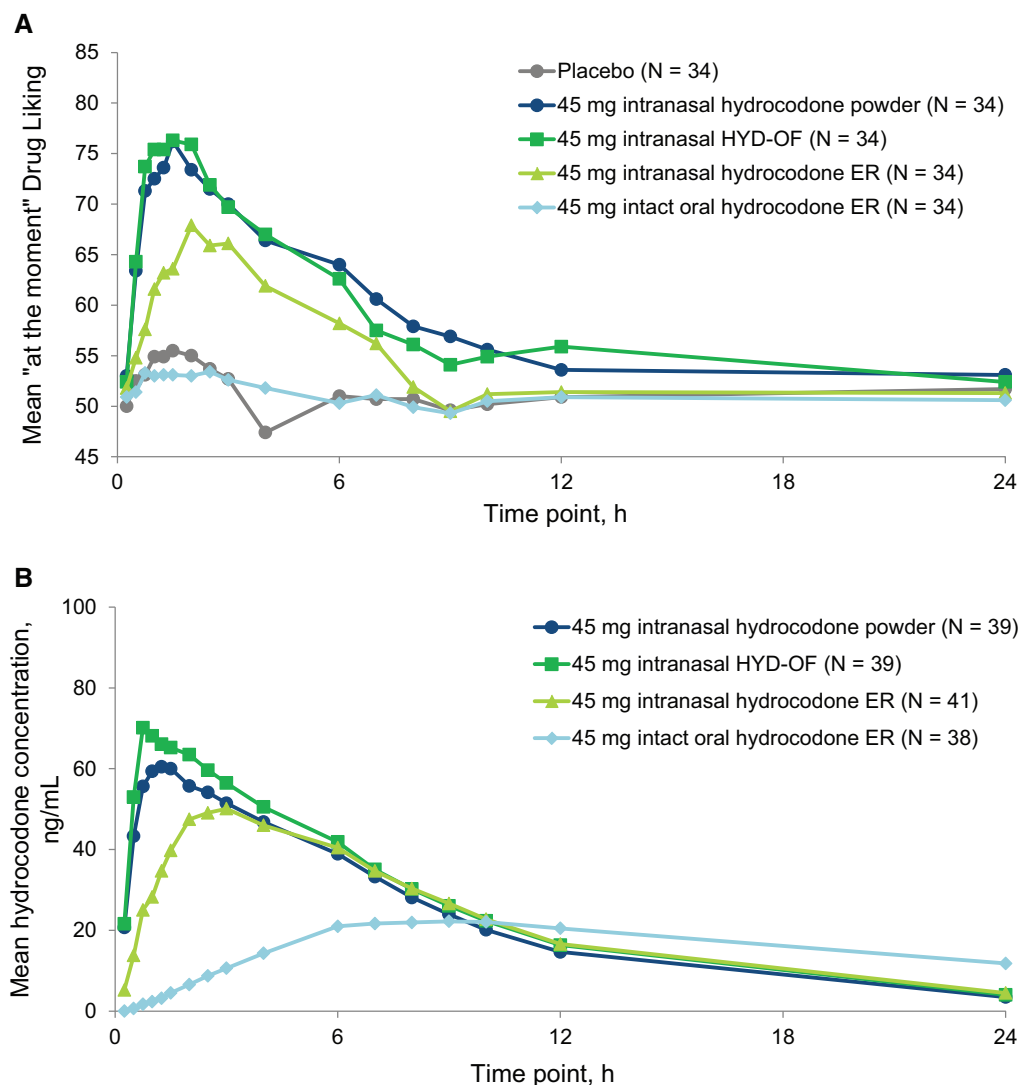


Figure 2 (A) Mean “at the moment” Drug Liking over time assessed by the Drug Liking and Effects Questionnaire (0–24 hours) and (B) mean plasma hydrocodone concentration over time (0–24 hours). ER = extended release; HYD-OF = non-abuse-deterrent hydrocodone ER–original formulation.

hydrocodone ER (60.6) compared with intranasal hydrocodone powder (71.7) and intranasal HYD-OF (71.2). However, intranasal hydrocodone powder and intranasal HYD-OF had significantly ($P < 0.001$) higher Overall Drug Liking VAS E_{min} compared with placebo (55.1), while intranasal hydrocodone ER was not significantly ($P = 0.269$) different from placebo but was significantly ($P = 0.048$) higher than intact oral hydrocodone ER (53.3).

Significant differences were observed for “at the moment” Drug Liking VAS $AUEC_{0-12h}$, with lower values for intranasal hydrocodone ER (685.3) compared with intranasal hydrocodone powder (751.0; $P < 0.0001$) and intranasal HYD-OF (746.1; $P = 0.0002$). The active intranasal treatments had significantly ($P \leq 0.0003$)

higher values than placebo (611.8), and intranasal hydrocodone ER had significantly ($P = 0.0004$) higher values than intact oral hydrocodone ER (613.7).

The TDAA is a bipolar VAS (neutral = 50) that assesses a subject’s willingness or desire to take the drug again. Subjects were significantly ($P \leq 0.005$) less likely to take intranasal hydrocodone ER (67.5) compared with intranasal hydrocodone powder (75.5) and intranasal HYD-OF (78.9). Willingness to take placebo (56.4) or intact oral hydrocodone ER (56.1) was scored significantly ($P < 0.001$) lower than the intranasal treatments.

The PVAQ requests that subjects select a specific dollar amount that they would be willing to pay for the drug. Similar to the results of other balance of effects end

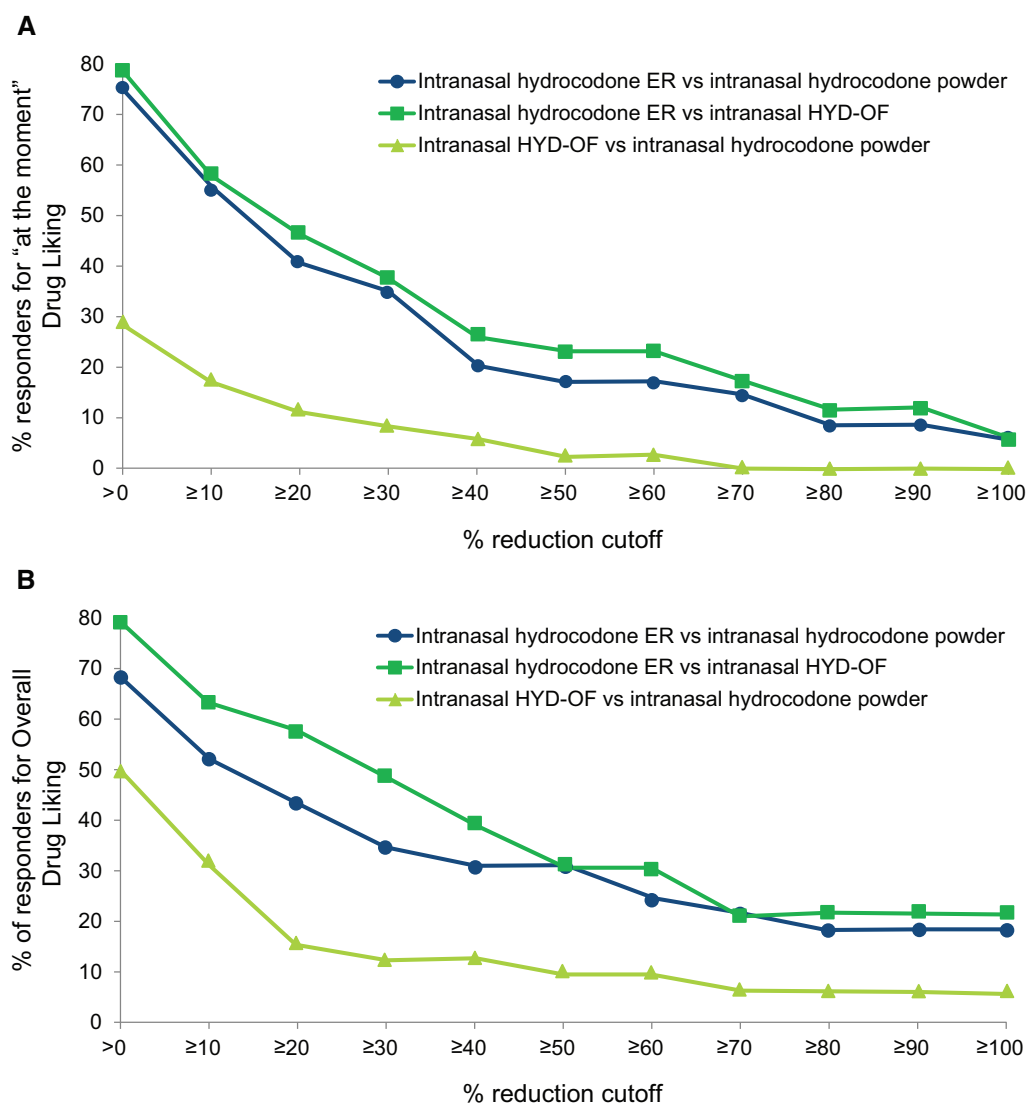


Figure 3 Proportion of responders for E_{\max} for (A) “at the moment” Drug Liking and (B) Overall Drug Liking. A responder was defined as a subject who demonstrated a desired percent reduction in E_{\max} for the test product relative to the control. E_{\max} = maximum effect; ER = extended release; HYD-OF = non-abuse-deterrent hydrocodone ER-original formulation.

points, PVAQ values were significantly ($P < 0.05$) lower for intranasal hydrocodone ER (8.8) compared with intranasal hydrocodone powder (11.3) and intranasal HYD-OF (12.6). Values for placebo (2.9) and intact oral hydrocodone ER (3.1) were significantly ($P \leq 0.0001$) lower than those for the intranasal treatments.

Measures of Positive and Negative Effects

The positive effects of the drug were measured by E_{\max} and AUEC of the Good Effects VAS and the Morphine-Benzedrine Group (MBG) subscale of the ARCI (Table 1). A marked increase in mean Good Effects VAS scores was observed with intranasal hydrocodone powder and intranasal HYD-OF, and the peak effect

occurred 1.5 hours postdose for both treatments (Figure 4). Over 0.75 and 4 hours postdose, intranasal HYD-OF was associated with higher scores than intranasal hydrocodone powder. Scores for intranasal hydrocodone ER showed a slower onset, with a peak at approximately 2.5 hours postdose, and lower scores continued through 10 hours postdose. Placebo and intact oral hydrocodone ER were associated with minimal change over time for Good Effects VAS scores. E_{\max} for Good Effects VAS was significantly ($P < 0.0001$) lower with intranasal hydrocodone ER (43.6) compared with intranasal hydrocodone powder (58.5) and intranasal HYD-OF (67.5). Similar results were obtained for AUEC_{0-48h}, with values of 255.5 vs 388.1 and 332.2, respectively ($P \leq 0.0007$).

Table 1 Mean (SD) scores on secondary pharmacodynamic measures of subjective drug effects by treatment

		Hydrocodone 45 mg				
Secondary Measure	Variable	Placebo (N = 34)	IN Hydrocodone Powder (N = 34)	IN HYD-OFF (N = 34)	IN Hydrocodone ER (N = 34)	Intact PO Hydrocodone ER Tablet (N = 34)
Measures of balance of effects	Drug Liking at given moment	44.3 (14.0)	46.8 (6.3)*	46.4 (10.6)*	42.9 (12.3)	47.0 (6.6)*
	Overall Drug Liking	611.8 (61.5)	751.0 (123.9)***	746.1 (129.6)***	685.3 (124.9)**	613.7 (45.6)*
	TDA	55.1 (11.7)	71.7 (16.0)***	71.2 (21.8)***	60.6 (19.3)	53.3 (13.7)*
	PVAQ	56.4 (12.4)	75.5 (15.0)***	78.9 (16.8)***	67.5 (20.1)**	56.1 (14.1)*
	Good Effects	2.9 (5.5)	11.3 (7.8)**	12.6 (10.2)***	8.8 (8.0)**	3.1 (7.2)*
Measures of positive effects	Good Effects	15.5 (22.6)	58.5 (27.5)***	67.5 (24.0)***	43.6 (26.6)**	12.6 (22.5)*
	MBG scale	59.1 (124.0)	388.1 (452.6)***	332.2 (204.5)***	255.5 (305.0)**	72.4 (152.3)*
	Bad Effects	3.9 (3.4)	7.1 (4.3)**	6.8 (4.2)**	6.3 (4.6)**	3.0 (2.5)*
	Nausea	55.9 (43.2)	63.6 (49.2)	70.6 (61.1)**	62.9 (56.6)	52.9 (48.8)
	LSD scale	4.9 (10.3)	14.8 (18.1)***	19.3 (23.6)**	22.7 (27.5)**	8.3 (13.8)*
Measures of negative effects	Nausea	27.8 (42.7)	110.0 (195.5)**	119.4 (206.5)**	121.9 (159.7)**	35.4 (55.2)*
	Ease of Snorting Score	4.3 (7.6)	14.8 (22.1)**	16.4 (23.4)**	15.1 (23.1)**	5.8 (13.9)*
	Burning	33.2 (78.4)	83.4 (127.3)**	81.6 (128.9)**	77.1 (139.7)**	36.3 (87.6)*
	Need to blow nose	4.2 (1.9)	6.2 (2.5)**	6.3 (2.6)**	5.8 (2.6)**	3.8 (1.3)*
	Runny nose/nasal discharge	76.5 (19.1)	94.1 (29.1)**	91.1 (35.5)**	90.5 (31.1)**	77.2 (22.6)*
Measures of nasal effects	Ease of Snorting Score	32.0 (23.8)	40.5 (25.1)	36.0 (27.3)	42.2 (26.8)	29.2 (22.4)*
	Burning	1 (1)	1 (1)**	2 (1)**	1 (1)	1 (1)
	Need to blow nose	0.6 (1.6)	0.7 (1.0)	1.1 (1.9)*	0.8 (2.2)	0.3 (0.8)
	Runny nose/nasal discharge	1.6 (1.2)	1.9 (1.1)	2.0 (1.2)	1.9 (1.2)	1.4 (1.2)*
	Facial pain/pressure	1.9 (3.2)	1.5 (1.7)	1.5 (1.6)	1.8 (2.4)	1.5 (2.3)
Measures of sedative effects	Nasal congestion	1.2 (1.0)	1.7 (1.1)**	1.8 (1.1)**	1.1 (1.1)	1.3 (1.2)
	Alertness/drowsiness	1.4 (2.1)	1.0 (1.0)	1.3 (1.4)	1.0 (1.5)	1.0 (1.3)
	PCAG scale	0.8 (1.1)	1.0 (1.0)	1.2 (1.2)**	1.1 (1.2)	0.5 (1.0)*
	Alertness/drowsiness	1.5 (4.3)	1.4 (2.6)	1.7 (3.0)	2.0 (3.9)	0.8 (1.7)*
	PCAG scale	1.9 (1.1)	1.5 (1.1)	1.7 (1.3)	1.8 (1.3)	1.3 (1.2)*
Measures of sedative effects	Alertness/drowsiness	2.5 (4.4)	1.5 (1.9)	1.8 (2.4)	2.4 (3.4)	1.6 (2.7)
	PCAG scale	39.6 (14.7)	27.2 (13.9)**	25.2 (14.4)***	32.8 (13.2)**	41.9 (11.6)*
	Alertness/drowsiness	2,500.9 (318.2)	2,386.8 (373.3)**	2,360.0 (325.2)**	2,412.6 (279.9)	2,486.3 (333.5)
	PCAG scale	4.7 (2.7)	7.9 (2.7)**	8.5 (3.1)**	7.5 (3.2)**	4.3 (2.5)*
	PCAG scale	70.4 (30.0)	115.3 (43.3)***	114.4 (45.0)**	98.6 (34.0)**	72.5 (31.9)*

(continued)

Table 1 Continued

		Hydrocodone 45 mg				
Secondary Measure	Variable	Placebo (N = 34)	IN Hydrocodone Powder (N = 34)	IN HYD-OF (N = 34)	IN Hydrocodone ER (N = 34)	Intact PO Hydrocodone ER Tablet (N = 34)
Measures of other effects	Any effects	15.5 (21.9)	61.2 (26.1) ^{*,**}	69.8 (22.5) ^{*,**}	47.7 (27.6) ^{**}	13.9 (20.3) [*]
	Pupil diameter	71.7 (156.1)	375.2 (339.2) ^{*,**}	368.9 (230.3) ^{*,**}	289.6 (257.5) ^{**}	78.5 (123.7) [*]
		5.5 (0.8)	3.3 (0.7) ^{**}	3.0 (0.5) ^{*,**,*}	3.4 (0.6) ^{**}	4.0 (0.8) [*]
		294.0 (34.8)	250.1 (36.8) ^{**}	249.9 (31.5) ^{**}	254.7 (30.5) ^{**}	250.6 (33.8)

AUEC_{0-x} = area under the effect curve from 0 to x hours; E_{max} = maximum effect; E_{min} = minimum effect; ER = extended release; HYD-OF = non-abuse-deterrent hydrocodone ER—original formulation; IN = intranasal; LSD = lysergic acid diethylamide; MBG = Morphine-Benzedrine Group; PCAG = Pentobarbital, Chlorpromazine, Alcohol Group; PO = oral; PVAQ = Price Value Assessment Questionnaire; TDAA = Take Drug Again Assessment.

*P < 0.05 vs IN hydrocodone ER.

**P < 0.05 vs placebo.

***P < 0.05 vs IN hydrocodone powder.

Positive subjective effects of the drugs were also evaluated with the MBG subscale of the ARCI, which uses true/false statements such as “I feel in complete harmony with the world and those about me” and “I would be happy all the time if I felt as I feel now.” ARCI MBG E_{max} was not significantly different between intranasal treatments, with values of 6.3 for intranasal hydrocodone ER, 7.1 for intranasal hydrocodone powder, and 6.8 for intranasal HYD-OF. All three intranasal treatments were significantly (P < 0.0006) different from placebo (3.9), and intranasal hydrocodone ER was significantly (P < 0.0001) higher than intact oral hydrocodone ER (3.0) for ARCI MBG E_{max}. Similarly, ARCI MBG AUEC_{0-24h} was not significantly different between intranasal treatments or between intranasal (62.9) and intact oral hydrocodone ER (52.9); however, a significant difference (P = 0.02) was observed between intranasal HYD-OF (70.6) and placebo (55.9).

Negative effects of the drugs were assessed through E_{max} and AUEC for Bad Effects VAS, Nausea VAS, and the LSD subscale of the ARCI (Table 1). Additional information on these results is available in the Supplementary Data, and mean Bad Effects VAS scores over time are shown in Figure S2.

Measures of Nasal Effects

One significant difference was observed in Ease of Snorting VAS between the oral hydrocodone ER treatment that consisted of the intranasal “dummy” treatment of sugar spheres and lactose (29.2) and intranasal hydrocodone ER (42.2, mean difference 12.58; P = 0.017) (Table 1). Additional information regarding nasal effects is summarized in the Supplementary Data.

Measures of Sedative Effects

Sedative effects of the treatments were measured by E_{min} and AUEC of the Alertness/Drowsiness VAS and Pentobarbital, Chlorpromazine, Alcohol Group (PCAG) subscale of the ARCI (Table 1). Additional information regarding sedative effects is summarized in the Supplementary Data.

Measures of Other Effects

The Any Effects VAS assessed whether the subject felt any drug effect. Mean Any Effects VAS scores were markedly increased beginning 0.5 hours after administration of intranasal hydrocodone powder and intranasal HYD-OF, with peak effects at 1.25 and 1.5 hours post-dose, respectively (Figure 5). Any Effects VAS scores for intranasal hydrocodone ER showed a slower onset, lower peak, and less sustained effect. Scores were similar after administration of intact oral hydrocodone ER and placebo. Any Effects VAS E_{max} and AUEC_{0-48h} were significantly (P < 0.006) lower with intranasal hydrocodone ER (47.7 and 289.6) compared with intranasal hydrocodone powder (61.2 and 375.2) and intranasal HYD-OF (69.8 and 368.9). Compared with

Intranasal Abuse Potential of Hydrocodone ER

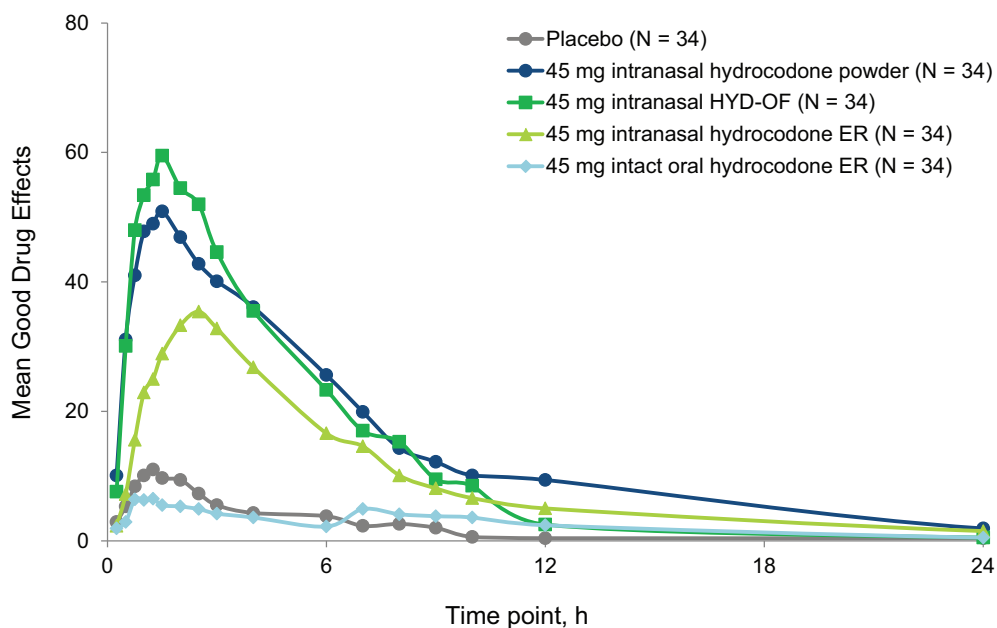


Figure 4 Mean Good Drug Effects over time assessed by the Drug Liking and Effects Questionnaire (0–24 hours). ER = extended release; HYD-OF = non-abuse-deterrent hydrocodone ER–original formulation.

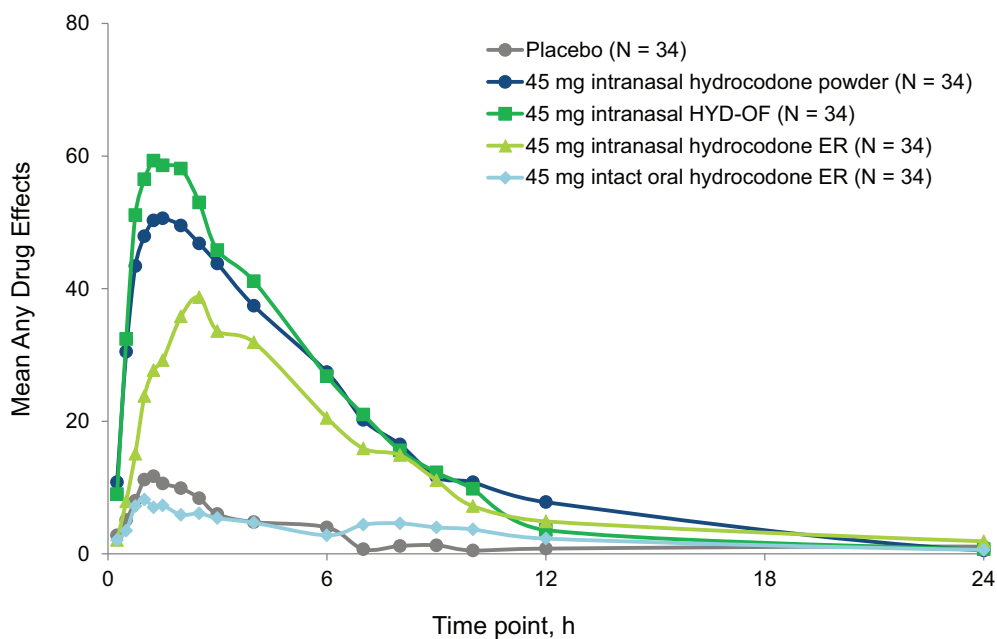


Figure 5 Mean Any Drug Effects over time assessed by the Drug Liking and Effects Questionnaire time (0–24 hours). ER = extended release; HYD-OF = non-abuse-deterrent hydrocodone ER–original formulation.

placebo (15.5 and 71.7), all active intranasal treatments showed significantly ($P < 0.001$) greater effects, and intranasal hydrocodone ER showed significantly ($P < 0.001$) greater effects than intact oral hydrocodone ER (13.9 and 78.5).

Pupillometry provided an objective measure of the physiologic effects of the treatments. Mean pupil diameter over 48 hours is shown in Figure S3 of the Supplementary Data. Pupillary constriction was slightly greater and showed a more rapid onset after

administration of intranasal hydrocodone powder and intranasal HYD-OF compared with intranasal hydrocodone ER. In contrast to other secondary measures, intact oral hydrocodone ER was associated with differences in pupillary constriction compared with placebo. Intact oral hydrocodone ER decreased pupil diameter with a much slower onset but longer duration than the other active treatments.

Mean E_{\min} for pupil diameter measurements for all three intranasal hydrocodone treatments were significantly ($P < 0.001$) lower than that of placebo, validating the physiologic effect of intranasal hydrocodone (Table 1). Pupil diameter E_{\min} was significantly greater after administration of intranasal hydrocodone ER (indicating less pupillary constriction; 3.4) compared with intranasal HYD-OF (3.0; $P = 0.006$), but it was not significantly different from intranasal hydrocodone powder (3.3).

Pharmacokinetics

Mean plasma hydrocodone concentration-time profiles over 24 hours for active treatments are shown in Figure 2B. The plasma concentration-time profile for each treatment resembled its corresponding profile for “at the moment” Drug Liking over time, shown in Figure 2A.

Table 2 summarizes the pharmacokinetic parameters for each active study treatment. C_{\max} was lowest for oral intact hydrocodone ER (25.1 ng/mL) and highest for intranasal HYD-OF (80.3 ng/mL). As expected, the rate of absorption of hydrocodone was slowest for oral intact hydrocodone ER, with a t_{\max} of 9.1 hours, compared with the t_{\max} for intranasal hydrocodone ER (2.6 hours), intranasal hydrocodone powder (1.4 hours), and intranasal HYD-OF (1.1 hours). Decline from peak plasma concentrations appeared to occur in a monophasic manner, with mean $t_{1/2}$ of 10 hours for oral intact hydrocodone ER and 5.6 to 6.2 hours for intranasal hydrocodone treatments.

Overall systemic exposures (as assessed by $AUC_{0-\infty}$ and AUC_{0-t}) were comparable after administration of intranasal hydrocodone ER and intranasal hydrocodone powder. However, peak hydrocodone plasma concentration was approximately 12% lower after administration of intranasal hydrocodone ER compared with intranasal hydrocodone powder. As a result of the lower and later peak value, early exposure, as assessed by $AUC_{0-t_{\max}}$, $IN(\text{powder})$ and $AUC_{0-t_{\max}}$, $ER(IN)$, to hydrocodone was notably lower for intranasal hydrocodone ER, by approximately 51% and 30%, respectively, compared with that of intranasal hydrocodone powder. Similar results were observed in the comparison of intranasal hydrocodone ER and intranasal HYD-OF pharmacokinetics. C_{\max} was approximately 22% lower for intranasal hydrocodone ER compared with intranasal HYD-OF, and as a result of lower early exposure, $AUC_{0-t_{\max}}$, $Zoh(IN)$ and $AUC_{0-t_{\max}}$, $ER(IN)$ were reduced by approximately 63% and 39%, respectively, with intranasal hydrocodone ER compared with intranasal HYD-OF.

Comparison of intranasal and intact oral hydrocodone ER pharmacokinetics showed that C_{\max} was approximately 134% higher after intranasal administration, which is consistent with the ER profile of hydrocodone for oral administration. Exposure to hydrocodone was higher after administration of intranasal hydrocodone ER compared with treatment with intact oral hydrocodone ER.

Consistent with the exposure findings, the AQ for intranasal hydrocodone ER was, on average, approximately 17% lower compared with intranasal hydrocodone powder and approximately 42% lower compared with intranasal HYD-OF. The AQ for intranasal hydrocodone powder showed considerable variability (% coefficient of variation [CV] = 92.72, range = 4.81–231.33 ng/mL/h), resulting in the wide 90% confidence intervals for this particular treatment comparison. The variability in AQ was lower for intranasal hydrocodone ER (% CV = 54.05, range = 5.14–61.63 ng/mL/h).

Plasma concentrations (assessed by C_{\max}) of hydromorphone were approximately 1% of those observed for hydrocodone after each treatment.

Safety and Tolerability

This study enrolled nondependent, recreational opioid users. No deaths or serious AEs were reported during the study. One subject was withdrawn from the treatment phase after administration of intranasal hydrocodone powder because of AEs of nausea and vomiting that interfered with drug administration. During the treatment phase, the overall incidence of AEs was lowest after placebo (18%), slightly higher after intact oral hydrocodone ER (24%), similar after intranasal hydrocodone powder (53%) and intranasal hydrocodone ER (52%), and highest after intranasal HYD-OF (61%). AEs reported during the treatment phase by at least 5% of subjects in any treatment group are summarized in Table 3. The majority of AEs were mild in severity and resolved.

No clinically relevant changes in serum chemistry, hematology, urinalysis, physical examination, or ECG findings were noted during the study. Overall, mean vital sign measurements and SpO_2 remained within the normal range throughout the study. There were isolated abnormalities in vital signs and SpO_2 that were considered potentially clinically significant according to prespecified criteria, but not considered clinically meaningful by the investigator with the exception of 1 AE of hypotension.

Discussion

Intranasal administration is a common route of prescription opioid abuse, particularly for ER formulations [13,14], because it may be associated with faster absorption and therefore greater subjective positive effects [5,21]. Thus, the intranasal route of administration is important to understanding the abuse potential of prescription hydrocodone ER formulations. In this study,

Table 2 Mean (SD) pharmacokinetic parameters for hydrocodone by treatment

Variable	Hydrocodone 45 mg			
	IN Hydrocodone Powder (N = 38)	IN HYD-OF (N = 39)	IN Hydrocodone ER (N = 41)	Intact oral Hydrocodone ER Tablet (N = 38)
C _{max} , ng/mL	71.28 (30.48)	80.27 (29.29)	56.84 (15.07)	25.05 (7.18)
t _{max} , h*	1.38 (0.60, 7.07)	1.12 (0.55, 6.17)	2.62 (1.33, 7.02)	9.11 (4.10, 12.12)
AUC _{0-∞} , ng·h/mL	579 (163)	639 (179)	572 (150)	568 (172)
AUC _{0-t} , ng·h/mL	576 (161)	637 (178)	568 (149)	531 (152)
AUC _{0-tmax} , IN(powder), ng·h/mL	57.5 (28.3)	66.5 (28.3)	24.9 (13.4)	1.9 (0.8)
AUC _{0-tmax} , ER(IN), ng·h/mL	125.9 (51.8)	142.4 (51.5)	78.5 (28.6)	9.4 (2.7)
AUC _{0-tmax} , ER(PO), ng·h/mL	380.0 (112.3)	416.3 (108.8)	336.4 (75.1)	127.5 (34.9)
AUC _{0-tmax} , Zoh(IN), ng·h/mL	39.3 (20.9)	46.4 (21.2)	15.1 (8.7)	1.0 (0.5)
Extrapolation, %†	0.60 (0.94)	0.38 (0.24)	0.73 (0.72)	6.04 (3.94)
λ _z , 1/h	0.124 (0.023)	0.127 (0.021)	0.114 (0.015)	0.076 (0.024)
t _{1/2} , h	5.78 (1.06)	5.58 (0.86)	6.16 (0.76)	9.96 (3.03)
Abuse quotient, ng/mL/h‡	59.6 (55.2)	75.4 (54.0)	22.6 (12.2)	3.1 (1.2)

AUC_{0-∞} = area under the plasma drug concentration by time curve (AUC) from time 0 to infinity; AUC_{0-t} = AUC from time 0 to the time of the last measurable drug concentration; AUC_{0-tmax}, IN(powder) = AUC from time 0 to the median t_{max} for intranasal hydrocodone powder; AUC_{0-tmax}, ER(IN) = AUC from time 0 to the median t_{max} for hydrocodone ER when finely milled and administered intranasally; AUC_{0-tmax}, ER(PO) = AUC from time 0 to the median t_{max} for hydrocodone ER when administered orally (intact); AUC_{0-tmax}, Zoh(IN) = AUC from time 0 to the median t_{max} for Zohydro when finely milled and administered intranasally; C_{max} = maximum observed plasma drug concentration; ER = extended release; HYD-OF = non-abuse-deterrent hydrocodone ER—original formulation; IN = intranasal; t_{1/2} = elimination half-life; t_{max} = time to maximum observed plasma drug concentration; λ_z = plasma terminal elimination rate constant.

*Values for t_{max} are median (range).

†Percent extrapolation = 100·(AUC_{0-∞}-AUC_{0-t})/AUC_{0-∞}.

‡Abuse quotient = C_{max}/t_{max}.

the abuse potential of hydrocodone ER, a hydrocodone bitartrate formulated with CIMA ADT to protect against rapid release of hydrocodone when the tablets are comminuted, was evaluated after intranasal administration of finely milled tablets. This is the second clinical abuse liability study of this hydrocodone ER formulation. In the first study, peak Drug Liking following oral administration of intact and finely milled hydrocodone ER tablets was associated with significantly ($P < 0.001$) lower abuse potential compared with oral hydrocodone powder in non-dependent recreational opioid users [16]. Similarly, the current study of intranasal administration included intranasal hydrocodone powder as well as intranasal finely milled HYD-OF (prior to reformulation) as active comparators. Placebo (included per FDA guidance to validate the study [18]) and intact oral hydrocodone ER (to present the product when used as intended) were also included in this randomized, double-blind, crossover study of nondependent recreational opioid users.

Intranasal administration of hydrocodone ER was associated with significantly lower scores for peak “at the moment” Drug Liking and Overall Drug Liking VAS compared with intranasal hydrocodone powder. Results of other secondary outcome measures, including balance of effects and positive effects, were consistent with the primary outcomes. Significantly higher peak “Bad Effects” were observed with intranasal hydrocodone ER compared with intranasal hydrocodone powder.

Moreover, the abuse potential of intranasal hydrocodone ER was also lower than that of a non-abuse-deterrent formulation of hydrocodone ER (HYD-OF) that was finely milled and administered intranasally. Intranasal HYD-OF was associated with similar or greater effects on the primary and secondary pharmacodynamic end points compared with intranasal hydrocodone powder, indicating that the potential for intranasal abuse with HYD-OF is similar to that for hydrocodone powder.

The intranasal abuse potential of IR and ER oxycodone abuse-deterrent formulations has been evaluated in similarly designed studies [5,21]. In a study of 27 recreational opioid users, intranasal administration of an abuse-deterrent formulation of oxycodone (OxyContin) was associated with significantly lower pharmacodynamic effects, including Overall Drug Liking, TDAA, and pupillometry, compared with positive controls [5]. The abuse-deterrent formulation showed a decrease in the rate and extent of oxycodone absorption in the first hours after intranasal administration. AQs were fivefold higher for oxycodone controls compared with the abuse-deterrent formulation. Another study compared the pharmacodynamic effects of an abuse-deterrent IR formulation of oxycodone with those of oxycodone IR when crushed and administered intranasally to 39 non-dependent, recreational opioid users [21]. Peak Drug Liking scores were significantly reduced with the abuse-deterrent formulation compared with oxycodone

Table 3 Adverse events occurring in $\geq 5\%$ of subjects in any treatment group during the treatment phase (safety analysis set)

AE, No. (%)	Hydrocodone 45 mg				
	Placebo (N = 39)	IN Hydrocodone Powder (N = 40)	IN HYD-OF (N = 41)	IN Hydrocodone ER (N = 42)	Intact oral Hydrocodone ER (N = 38)
≥ 1 AE*	7 (18)	21 (53)	25 (61)	22 (52)	9 (24)
Nausea	2 (5)	7 (18)	7 (17)	10 (24)	2 (5)
Vomiting	1 (3)	4 (10)	10 (24)	8 (19)	1 (3)
Headache	1 (3)	1 (3)	3 (7)	8 (19)	2 (5)
Pruritus, generalized	0	7 (18)	6 (15)	6 (14)	0
Pruritus	0	7 (18)	10 (24)	3 (7)	1 (3)
Euphoric mood [†]	2 (5)	1 (3)	5 (12)	3 (7)	0
Dizziness	0	0	3 (7)	3 (7)	1 (3)
Tremor	0	0	2 (5)	1 (2)	0
Hot flush	1 (3)	1 (3)	2 (5)	1 (2)	0
Somnolence	2 (5)	2 (5)	3 (7)	0	0
Hiccups	0	2 (5)	3 (7)	0	0
Irritability	0	3 (8)	0	0	0

AE = adverse event; ER = extended release; HYD-OF = non-abuse-deterrent hydrocodone ER—original formulation; IN = intranasal.

*Subjects may have reported one or more AEs.

[†]Euphoric mood was only recorded as an adverse event if spontaneously reported by the subject, not based on the pharmacodynamic measures.

IR (70.8 vs 93.5; $P < 0.0001$), and similar results were obtained for Overall Drug Liking and TDAA. It is important to note that these studies represent available premarketing methods to assess the potential impact of abuse-deterrent formulations on abuse. The magnitude of change needed to demonstrate clinically meaningful improvement is not well established at this time and requires further research. Postmarketing epidemiology studies are needed to confirm the impact of abuse-deterrent opioid formulations on abuse in the real-world setting.

The results of these studies of intranasal oxycodone abuse potential are consistent with those of the present study of intranasal administration of finely milled hydrocodone ER tablets and a previous study of oral administration of intact and finely milled hydrocodone ER [16]. In both studies, hydrocodone ER formulated with ADT was associated with significant decreases in drug likability and effect measures compared with controls. However, as intact oral hydrocodone ER behaves similarly to placebo, there was a significant difference in most drug likeability and effect measures when comparing crushed or finely milled hydrocodone ER to intact hydrocodone ER, suggesting that potential abuse cannot be fully eliminated.

The pharmacodynamics time course profile of intranasal hydrocodone ER was markedly different from those of intranasal hydrocodone powder and intranasal HYD-OF. Intranasal hydrocodone ER had a slower rate of rise and later onset, with a lower peak effect and more

transient effects overall compared with the other active intranasal treatments. These results were consistent with the pharmacokinetic profiles of each treatment and demonstrate that the subjective effects generally parallel hydrocodone plasma concentrations after intranasal administration. Overall systemic exposure to hydrocodone was comparable for all active treatments except intranasal HYD-OF, which resulted in greater overall exposure. Peak plasma concentrations were highest after intranasal HYD-OF, followed by intranasal hydrocodone powder, and the C_{max} of intranasal hydrocodone ER was approximately 22% lower than that of intranasal HYD-OF. The time to reach peak plasma concentration of hydrocodone was delayed with intranasal hydrocodone ER compared with both intranasal hydrocodone powder and intranasal HYD-OF. AQs for intranasal hydrocodone ER were approximately 17% and 42% lower than those of intranasal hydrocodone powder and intranasal HYD-OF, respectively. These findings suggest that hydrocodone ER retained some of its ER properties despite manipulation to the limits of the formulation (i.e., worst case in terms of tampering methods).

Nasal effects of the treatments were modest, ranging from no problem to mild problems, and although some statistical differences were observed, they are unlikely to be clinically relevant. Hydrocodone ER was not associated with new safety issues. The overall incidence of AEs was similar between intranasal hydrocodone ER and intranasal hydrocodone powder, but slightly higher after intranasal HYD-OF.

This study was designed and conducted with consideration of the FDA guidance on abuse-deterrent opioids at the time [18]. To control for within-subject variability, a crossover design was used, and both active and placebo controls were included. Subjects were required to have a history of recreational opioid use, including experience with intranasal administration. The qualification phase ensured that the subjects could distinguish between hydrocodone and placebo. Despite adherence to guidelines and proper use of controls, abuse potential studies are limited by relatively small sample sizes and controlled settings that do not necessarily generalize to the at-risk population and opioid-dependent individuals. Other real-world factors may play a role in opioid abuse, such as cost, accessibility, peer influence, and mechanisms of abuse. The FDA recommends evaluation of postmarketing data to determine the impact of abuse-deterrent formulations on actual abuse [4].

Conclusions

The findings from this study of intranasal administration, along with results from a previous study assessing oral administration [16], have demonstrated a significantly lower abuse potential with hydrocodone ER tablets formulated with CIMA ADT compared with hydrocodone controls via the two most common routes of hydrocodone abuse [13,14]. Subjective effects of “at the moment” Drug Liking and Overall Drug Liking VAS were reduced with intranasal hydrocodone ER compared with intranasal hydrocodone powder and intranasal HYD-OF. Intranasal hydrocodone ER was associated with a slower onset and rate of rise, a lower peak, and a shorter duration of effects compared with intranasal hydrocodone powder and intranasal HYD-OF. The pharmacokinetic profile of intranasal hydrocodone ER was consistent with its pharmacodynamic effects, and together these findings demonstrate a lower abuse potential compared with non-abuse-deterrent formulations of hydrocodone. No new safety issues were observed. The effects of intact oral hydrocodone ER were similar to those of placebo. When hydrocodone ER tablets were finely milled and administered intranasally, the onset of drug effect was delayed and subjective effects were reduced, further suggesting that the drug’s attractiveness for abuse may be reduced.

Supplementary Data

Supplementary data are available at *Pain Medicine* online.

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