Effects of Paroxetine, a CYP2D6 Inhibitor, on the Pharmacokinetic Properties of Hydrocodone After Coadministration With a Single-entity, Once-daily, Extended-release Hydrocodone Tablet

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ABSTRACT

Purpose: A single-entity, once-daily, extended-release formulation of hydrocodone bitartrate (HYD) has been developed for the management of moderate to severe chronic pain. Hydrocodone undergoes cytochrome P-450 (CYP)-mediated metabolism involving the CYP3A4 and CYP2D6 isozymes. CYP3A4 yields norhydrocodone, a major inactive metabolite, whereas CYP2D6 yields hydromorphone, a minor active metabolite. This study examined the influence of the coadministration of paroxetine, a strong selective CYP2D6 inhibitor, on the pharmacokinetic properties of hydrocodone (and hydromorphone) in healthy adults.

Methods: In this randomized, double-blind, 2-period, 2-treatment crossover study, 24 healthy subjects received paroxetine 20 mg or placebo once daily for 12 days and an HYD 20-mg tablet on day 10 of each period.

Findings: Hydrocodone mean Cmax and t½ and median Tmax values were similar with paroxetine or placebo coadministration (16.8 vs 15.9 ng/mL, 8.5 vs 8.4 hours, and 18.0 vs 18.0 hours, respectively), as were mean AUC0–t and AUC0–1 values (342.9 vs 325.3 ng · h/mL and 346.3 vs 328.5 ng · h/mL). The 90% CIs of the geometric mean ratios of the hydrocodone AUC and Cmax values were fully within the predetermined range of 80% to 125%, suggesting that there was no effect of multiple doses of paroxetine on systemic exposure to hydrocodone. Mean hydromorphone AUC0–t and Cmax values were decreased with paroxetine versus placebo (0.64 vs 3.8 ng · h/mL and 0.06 vs 0.19 ng/mL), whereas Tmax values remained similar (18.0 vs 16.1 hours, respectively). The mean hydromorphone AUC0–∞ value could not be calculated. Both regimens were well tolerated; after HYD administration, the numbers of adverse events were similar between the 2 treatment regimens, and all adverse events were mild.

Implications: In this study, the coadministration of single-dose HYD with paroxetine at steady state did not alter systemic exposure to hydrocodone, suggesting that HYD can be coadministered with CYP2D6 inhibitors at therapeutic doses, without dosage modification. (Clin Ther. 2015;37:2286–2296) © 2015 The Authors. Published by Elsevier HS Journals, Inc.

Key words: CYP2D6 inhibitor, drug–drug interaction, hydrocodone, hydromorphone, opioid, paroxetine, pharmacokinetics.

INTRODUCTION

Hydrocodone is a semisynthetic opioid that produces analgesic activity primarily via μ-receptor agonism. The pharmacologic and pharmacokinetic (PK) properties of hydrocodone are characteristic of many opioid analgesics, and the relative analgesic potency of hydrocodone is considered to be approximately equivalent to that of oxycodone and twice that of oral morphine.1,2

The data from this paper were previously presented in poster format at PAINWeek 2013. The abstract was submitted and accepted at PAINWeek, and published at their online forum, Las Vegas, Nevada, September 4–7, 2013.

Accepted for publication August 1, 2015.
http://dx.doi.org/10.1016/j.clinthera.2015.08.007 0149-2918 $ - see front matter
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In the United States, hydrocodone is often combined with a nonopioid drug, such as acetaminophen or ibuprofen. Hydrocodone/acetaminophen combination products are the most commonly prescribed drugs in the United States, with an estimated 129.2 million prescriptions in 2013. In October 2013, the use of a single-entity, twice-daily, extended-release formulation of hydrocodone bitartrate was approved by the US Food and Drug Administration. In November 2014, a single-entity, once-daily, extended-release tablet formulation of hydrocodone bitartrate (HYD*) was approved by the US Food and Drug Administration for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. HYD, an extended-release formulation, is available in multiple tablet strengths (20–120 mg) and does not contain a nonopioid component, permitting the treatment of chronic pain that requires higher total daily opioid doses. Additionally, HYD incorporates a proprietary extended-release technology that provides physicochemical attributes intended to impart abuse-deterrent properties.

Hydrocodone undergoes extensive cytochrome P-450 (CYP)-mediated oxidative metabolism involving CYP3A4-mediated N-demethylation, yielding norhydrocodone (major inactive metabolite; ~40% of circulating parent drug) and CYP2D6-mediated O-demethylation, yielding hydromorphone (minor active metabolite; up to 3% of circulating parent drug) (Figure 1). When hydrocodone was administered as a single oral dose of 15 mg, of the overall dose, urinary excretion values of the parent drug and its metabolites were as follows: hydrocodone, 11%; hydromorphone, 3.5%; norhydrocodone, 5.2%; and other metabolites (eg, 6-α/β-hydroxy metabolites), <3%. The mean total recovery values of hydrocodone and its metabolites were 25.7% and 13.2%, respectively. Other CYP isoforms, including 2B6, 2C9, 2C19, and 2E1, are minor contributors to hydrocodone metabolism.

The effects of the concurrent administration of CYP2D6 inhibitors with HYD on the tolerability of HYD have not been established. Paroxetine, a selective serotonin reuptake inhibitor used for treating depression in children and adults, is a strong selective CYP2D6 inhibitor.

Although the effects of CYP2D6 inhibition on hydrocodone exposure are not expected to be clinically meaningful, this hypothesis remains to be confirmed, considering the prevalence of multidrug exposure among patients taking opioids. This study examined the influence of CYP2D6 inhibition by paroxetine at steady state on the PK properties of hydrocodone and its minor active metabolite hydromorphone after the administration of a single dose of oral HYD in healthy adults.
SUBJECTS AND METHODS

Study Design

This single-center (PPD Phase I Clinic, Austin, TX), randomized, double-blind, 2-period, 2-treatment, 2-way crossover, drug–drug interaction study evaluated the effects of CYP2D6 inhibition on the PK properties of hydrocodone after the oral administration of HYD in healthy adults (Figure 2). The primary objective was to evaluate the PK properties of hydrocodone in the presence and absence of paroxetine. The secondary objective was to assess the tolerability of the concurrent administration of HYD and paroxetine in healthy adults.

Subjects were randomly assigned, in a 1:1 ratio, to receive either HYD + paroxetine (A) or HYD + placebo (B) in period 1 (days 1–12), followed by crossover to the alternate treatment in period 2 (days 14–25). Paroxetine 20-mg tablets or placebo tablets were administered once daily in the morning after an overnight fast, on every day of each period. A single HYD 20-mg tablet was administered once in each period (day 10 or 23) after an overnight fast. To avoid carryover effects, adequate study medication washout periods were built into the study design, based on each drug’s terminal half-life. In subjects assigned to receive paroxetine in period 1, there were 4 days between HYD dosing in period 1 (day 10) and the administration of the first dose of paroxetine in period 2 (day 14). Subjects entered the study unit and were randomized before paroxetine dosing on day 1 and remained confined to the study unit until the end of period 2.

The protocol and informed-consent form were reviewed and approved by the IntegReview institutional review board (Austin, Texas) before subjects were screened for entry into the study. The study was conducted in compliance with the International Conference on Harmonisation E6 Good Clinical Practice guideline and the US Code of Federal Regulations guideline. All subjects provided written informed consent.

Sample Size

No formal sample size calculations were performed; it was expected that the randomization of 24 subjects would provide sufficient treatment replications.

Study Population

Healthy subjects 18 to 50 years of age could enroll if they had a body weight ranging from 50 to 100 kg and a body mass index ranging from 18 to 30 kg/m²; were willing to eat the food supplied during the study, refrain from strenuous exercise through the end-of-study visit, and avoid beginning a new exercise program or participating in any unusually strenuous physical exertion; and had no significant abnormal findings on medical history taking, physical examination, clinical

Trademark: Paxil® (GlaxoSmithKline, Research Triangle Park, North Carolina).
laboratory analysis, vital sign measurement, and 12-lead ECG. In addition, female subjects of childbearing age who were not pregnant or breastfeeding were required to use an adequate and reliable method of contraception (ie, barrier with additional spermicidal foam or jelly, intrauterine device, or hormonal contraception), and female subjects who were postmenopausal for at least 1 year were required to have an elevated serum follicle-stimulating hormone level.

Subjects were excluded from the study for the following reasons: current or recent (within 5 years) history of drug or alcohol abuse; history or any current conditions that may have interfered with drug absorption, distribution, metabolism, or excretion; use of an opioid-containing medication in the 30 days preceding the administration of the first dose of study medication; known sensitivity to hydrocodone, paroxetine, or related compounds; history of depression or other history with an increased potential for suicide; history of frequent nausea or emesis regardless of etiology; history of seizures or head trauma with sequelae; participation in a clinical study in the 30 days preceding the administration of the first dose of study medication; any significant illness in the 30 days preceding the administration of the first dose of study medication; any personal or family history of a prolonged QT interval or cardiac rhythm disorders; and/or abnormal cardiac conditions (corrected QT interval $\geq 450$ ms at screening or corrected QT interval $\geq 480$ ms or greater during the treatment period).

Subjects were also excluded if they refused to abstain from food intake for 10 hours before dosing and 4 hours after dosing of HYD with paroxetine or placebo; caffeine- or xanthine-containing beverages entirely during confinement; alcoholic beverages for 7 days preceding the administration of the first dose of study medication and throughout the study; over-the-counter or prescription medications, including thyroid hormonal therapy (hormonal contraception and hormone-replacement therapy in the form of estrogen with or without progestin was allowed), vitamins, or dietary/herbal/mineral supplements for 7 days preceding the administration of the first dose of study medication and throughout the study; and/or any reason(s) for which the investigator deemed the subject unsuitable for inclusion in the study.

**Sample Collection**

Blood samples used for the quantification of the plasma concentration of hydrocodone were collected predose on days 10 and 23 and at 0.5, 1, 2.5, 4, 6, 8, 10, 12, 14, 16, 18, 24, 30, 36, 48, 72, and 80 hours after HYD dosing. Blood samples used for the quantification of the plasma concentration of paroxetine were collected before HYD dosing on days 10 and 23.

**Bioanalytical Methods**

Human plasma (K$_2$EDTA as an anticoagulant) was analyzed for hydrocodone, hydromorphone, and norhydrocodone and the internal standards (hydrocodone-d$_3$, hydromorphone-d$_6$ and norhydrocodone-d$_3$.HCl) using high-performance liquid chromatography with column switching and tandem mass spectrometry detection using positive ion electrospray. The assay was found to be linear from 0.1 to 100 ng/mL for hydrocodone and norhydrocodone, and from 0.05 to 50 ng/mL for hydromorphone, based on a 100-$\mu$L sample.

**Pharmacokinetic Assessments**

In each subject, the following PK parameters were calculated based on the plasma concentration of hydrocodone: $\text{AUC}_{0-\infty}$ calculated by the linear trapezoidal method; $\text{AUC}_{0-\infty}$ calculated as $\text{AUC}_{0-\infty} + C_t/\lambda_z$, where $C_t$ was the last measurable plasma concentration and $\lambda_z$ was the apparent terminal-phase rate constant; $C_{\text{max}}$; $T_{\text{max}}$ and $t_{1/2}$, where $t_{1/2}$ was the apparent terminal-phase half-life.
**Tolerability Assessments**

Tolerability was assessed based on the recording of adverse events (AEs), assessed using clinical laboratory tests (biochemistry, hematology, and urinalysis), vital sign measurements, oxygen saturation measurements, ECG results, and findings determined on physical examination. All AEs were coded using the terms from the *Medical Dictionary for Regulatory Activities* version 15.0 and were assessed by the investigator for severity and relatedness to study medication.

At the end of the study (80 hours postdose, end of period 2) or early discontinuation, the following were conducted: routine physical examination, vital sign assessment, blood and urine collection for laboratory tests, serum pregnancy test for women, and ECG. Concurrent medications and AEs were recorded. Any case of emesis was documented by the study staff. Seven to 10 days after the administration of the final dose of study medication, subjects were contacted by phone to determine the presence of any AEs.

**Pharmacokinetic Assessments**

PK properties were calculated, based on the plasma concentration of hydrocodone, by noncompartmental PK analysis (model-independent approach) using Phoenix WinNonlin version 6.2.1. (Pharsight Corporation, St. Louis, Missouri). Plasma concentrations less than the lower limit of quantification were set to 0 in the concentration summary, plots, and PK parameter calculations. Concentrations below the lower limit of quantification at the end of the PK profile were included in the calculations.

**Statistical Analysis**

The PK properties with the 2 treatment regimens were summarized using descriptive statistics, which included sample sizes, means (SD), %CVs, medians (range), and geometric means.

Statistical analysis of the effects of paroxetine on hydrocodone and hydromorphone PK properties was performed using an ANOVA model on the natural logarithms (ln) of the parameters, with treatment, sequence, and period as fixed effects and subject within sequence as a random effect. The analysis was performed using the following linear mixed model:

\[
\text{Parameter} = \text{Sequence} + \text{Subject (sequence)} + \text{Period} + \text{Treatment} + \text{Random error} + h \quad (1)
\]

For hydrocodone and hydromorphone, a comparison of the ln-transformed AUC\(_{0-t}\), AUC\(_{0-\infty}\), and C\(_{\text{max}}\) values (calculated when possible) in the presence and absence of paroxetine was performed. Geometric mean ratios (90% CIs) of the AUC\(_{0-t}\), AUC\(_{0-\infty}\), and C\(_{\text{max}}\) values were calculated when possible.

**RESULTS**

**Subjects**

Among the 54 healthy subjects screened, 24 subjects were randomized (Figure 3). Twenty-three subjects completed the study; 1 subject discontinued during period 2 due to personal choice. The full analysis population included 24 subjects, as did the per-protocol population. The baseline demographic and clinical characteristics of the per-protocol population are presented in Table I. Overall, the mean age of the subjects was 36.0 years, subjects were predominantly white (63%), and equal numbers of men and women were in the study (50% each). The baseline characteristics of the 2 treatment groups were similar (Table I).

**Pharmacokinetic Results**

The descriptive statistics of the PK properties of hydrocodone and hydromorphone are summarized in Table II. The mean C\(_{\text{max}}\) and t\(_{1/2}\) and median T\(_{\text{max}}\) values of hydrocodone were similar in the presence and absence of paroxetine (16.8 vs 15.9 ng/mL, 8.5 vs
Table I. Baseline demographic and clinical characteristics (per-protocol population).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>AB (n = 12)</th>
<th>BA (n = 12)</th>
<th>All Patients (N = 24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Mean (SD), y</td>
<td>35.7 (8.80)</td>
<td>36.3 (7.79)</td>
</tr>
<tr>
<td>Group, no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18–&lt;40 y</td>
<td>6 (50)</td>
<td>7 (58)</td>
<td>13 (54)</td>
</tr>
<tr>
<td>40–50 y</td>
<td>6 (50)</td>
<td>5 (42)</td>
<td>11 (46)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>6 (50)</td>
<td>6 (50)</td>
<td>12 (50)</td>
</tr>
<tr>
<td>Race, no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>8 (67)</td>
<td>7 (58)</td>
<td>15 (63)</td>
</tr>
<tr>
<td>Black or African American</td>
<td>3 (25)</td>
<td>4 (33)</td>
<td>7 (29)</td>
</tr>
<tr>
<td>Native American or Native Alaskan</td>
<td>1 (8)</td>
<td>0</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Other</td>
<td>0</td>
<td>1 (8)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Ethnicity, no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hispanic or Latino</td>
<td>6 (50)</td>
<td>4 (33)</td>
<td>10 (42)</td>
</tr>
<tr>
<td>Non-Hispanic or Non-Latino</td>
<td>6 (50)</td>
<td>8 (67)</td>
<td>14 (58)</td>
</tr>
<tr>
<td>Height, mean (SD), cm</td>
<td>169.2 (10.20)</td>
<td>167.8 (7.57)</td>
<td>168.5 (8.81)</td>
</tr>
<tr>
<td>Weight, mean (SD), kg</td>
<td>76.9 (11.63)</td>
<td>71.6 (12.28)</td>
<td>74.3 (12.02)</td>
</tr>
<tr>
<td>Body mass index, mean (SD), kg/m²</td>
<td>26.8 (2.86)</td>
<td>25.3 (2.66)</td>
<td>26.1 (2.81)</td>
</tr>
</tbody>
</table>

A = hydrocodone bitartrate 20 mg + paroxetine 20 mg; B = hydrocodone bitartrate 20 mg + placebo.

Table II. Pharmacokinetic properties of hydrocodone (full analysis population). * Data are given as mean (SD) unless otherwise noted.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Hydrocodone Bitartrate 20 mg + Paroxetine (n = 23)</th>
<th>Hydrocodone Bitartrate 20 mg + Placebo (n = 24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrocodone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$AUC_{0-t}$, ng · h/mL</td>
<td>342.9 (79.31)</td>
<td>325.3 (84.99)</td>
</tr>
<tr>
<td>$AUC_{0-\infty}$, ng · h/mL</td>
<td>346.3 (79.34)</td>
<td>328.5 (85.31)</td>
</tr>
<tr>
<td>$C_{\text{max}}$, ng/mL</td>
<td>16.8 (4.75)</td>
<td>15.9 (4.83)</td>
</tr>
<tr>
<td>$T_{\text{max}}$, median (range), h</td>
<td>18.0 (12.2–24.0)</td>
<td>18.0 (10.0–24.0)</td>
</tr>
<tr>
<td>$t_{50}$, h</td>
<td>8.5 (2.48)</td>
<td>8.4 (3.39)</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$AUC_{0-t}$, ng · h/mL</td>
<td>0.64 (0.748)</td>
<td>3.8 (2.51)</td>
</tr>
<tr>
<td>$AUC_{0-\infty}$, ng · h/mL</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>$C_{\text{max}}$, ng/mL</td>
<td>0.06 (0.052)</td>
<td>0.19 (0.119)</td>
</tr>
<tr>
<td>$T_{\text{max}}$, median (range), h</td>
<td>18.0 (12.0–24.0)</td>
<td>16.1 (12.0–24.0)</td>
</tr>
<tr>
<td>$t_{50}$, h</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

NA = not available.

*For hydromorphone, the majority of subjects had a lower limit of quantification (LLOQ) (0.05 ng/mL) or near-LLOQ across the concentration–time profile. Therefore, these results were not reported.
8.4 hours, and 18.0 vs 18.0 hours, respectively). Furthermore, the mean AUC0–t and AUC0–∞ values were similar in the presence and absence of paroxetine (342.9 vs 325.3 ng · h/mL and 346.3 vs 328.5 ng · h/mL). For hydromorphone, the administration of paroxetine decreased the mean AUC0–t value (0.64 vs 3.8 ng · h/mL) and the mean Cmax value (0.06 vs 0.19 ng/mL) relative to placebo. The mean hydrocodone Cmax and AUC values in the presence and absence of paroxetine are presented in Figure 4.

The mean plasma concentration–time profiles of hydrocodone and hydromorphone were similar regardless of the presence of paroxetine (Figure 5). The geometric least squares mean ratios ([HYD with paroxetine]/[HYD without paroxetine]) and 90% CIs of the hydrocodone AUC and Cmax values were 105.9% (97.7–114.6) and 106.0% (92.7–121.2), respectively, which were within the predetermined range of 80% to 125%, suggesting that steady-state paroxetine did not affect systemic hydrocodone exposure when coadministered with HYD (Table III).

**Tolerability**

A summary of AEs is presented in Table IV. All AEs were mild in intensity and resolved by the end of the study. The numbers of post-HYD treatment-related AEs were similar between the 2 treatment regimens (ie, HYD + paroxetine vs HYD + placebo). No deaths, serious AEs, or early discontinuations due to AEs were reported. In addition, there were no clinically significant changes in ECG results, clinical laboratory values, vital sign measurements, or oxygen saturation measurements for either treatment (paroxetine vs placebo) before or after HYD administration.

**DISCUSSION**

The effects of the concurrent administration of HYD and a CYP2D6 inhibitor on the tolerability and PK properties of hydrocodone have not been established in the clinic. This study examined the influence of CYP2D6 inhibition by paroxetine (a strong CYP2D6 inhibitor) at steady state on the PK properties of hydrocodone and its minor active metabolite.
hydromorphone after a single oral dose of HYD 20-mg extended-release tablets. Because the magnitude of the interaction with paroxetine was not known, a 20-mg single dose of HYD was selected so that it could be administered without the need for naltrexone blockade in healthy subjects.

The CYP3A4 pathway leading to norhydrocodone and the CYP2D6 pathway leading to hydromorphone are major and minor routes of hydrocodone metabolism, respectively. In addition to CYP2D6 and CYP3A4, CYP isoforms 2B6, 2C9, 2C19, and 2E1 are minor contributors. As such, the concurrent administration of either a CYP2D6 or CYP3A4 inhibitor may increase systemic exposure to hydrocodone.

CYP2D6 inhibition has been reported to alter the disposition and response to certain medications. For example, previous studies have shown that the inhibition of the CYP2D6 pathway using paroxetine was associated with a decreased metabolism of methadone, and with perphenazine, led to increased plasma concentrations and central nervous system effects. Furthermore, PK drug–drug interactions have been reported with the use of paroxetine and the CYP2D6 substrate metoprolol.

Although hydromorphone is an active metabolite, the systemic exposure of hydromorphone without CYP2D6 inhibition is only up to 3% of parent hydrocodone. This finding is consistent with those from previously published reports. Consequently, the inhibition of the minor CYP2D6-mediated pathway was expected to result in a minimal increase in systemic exposure to hydrocodone.

In the present study, the geometric mean ratios ([HYD with paroxetine]/[HYD without paroxetine]) of hydrocodone AUC and Cₘₐₓ values were 105.9% (90% CI, 97.7–114.6) and 106.0% (90% CI, 92.7–121.2), respectively. The absence of a significant change in the systemic levels of hydrocodone in the presence of paroxetine reaffirms that the CYP2D6 metabolism of hydrocodone to hydromorphone is a minor pathway. The mean hydromorphone AUC₀–ₖ and Cₘₐₓ values were less with paroxetine administration compared with placebo (0.64 vs 3.8 ng · h/mL and 0.06 vs 0.19 ng/mL, respectively), whereas the median Tₘₚ₇ values were similar (18.0 vs 16.1 hours, respectively). The mean hydromorphone AUC₀–∞ value could not be calculated. Single doses of 20-mg HYD administered in the presence or absence of paroxetine at steady state (20 mg once daily for 12 days) were well tolerated. These results are included in the HYD full prescribing information.

Although the oral analgesic potency of hydromorphone, compared with hydrocodone, is 2.5-fold, a low systemic exposure (∼3%) of hydromorphone would be expected to contribute minimally to the analgesic activity of hydrocodone. Therefore, CYP2D6 inhibition in a clinical setting is anticipated to have a minimal effect on the pharmacodynamic properties of hydrocodone.

Polymorphic variants of CYP2D6 are known to affect the metabolism of many drugs and can thereby influence drug disposition and therapeutic response. Approximately 7% of the white US population and 2% to 7% of the black US population are poor metabolizers of CYP2D6 substrates. Relative to extensive metabolizers, poor metabolizers exhibit

Figure 5. Mean (SD) plasma concentration–time profiles of hydrocodone (A) and hydromorphone (B) after the single-dose administration of hydrocodone 20 mg in the presence and absence of paroxetine.
### Table III. Geometric least squares (LS) mean* pharmacokinetic values of hydrocodone in plasma (full analysis population).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Hydrocodone Bitartrate 20 mg + Paroxetine (n = 23)</th>
<th>Hydrocodone Bitartrate 20 mg + Placebo (n = 24)</th>
<th>Ratio (%) of Geometric LS Means†</th>
<th>90% CI for Ratio‡</th>
<th>Intrasubject %CV</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC&lt;sub&gt;0–t&lt;/sub&gt;, ng · h/mL</td>
<td>332.9</td>
<td>314.5</td>
<td>105.9</td>
<td>97.7–114.6</td>
<td>15.9</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0–∞&lt;/sub&gt;, ng · h/mL</td>
<td>336.5</td>
<td>317.8</td>
<td>105.9</td>
<td>97.8–114.6</td>
<td>15.7</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt;, ng/mL</td>
<td>16.1</td>
<td>15.2</td>
<td>106.0</td>
<td>92.7–121.2</td>
<td>27.1</td>
</tr>
</tbody>
</table>

*Analysis of variance. Natural logarithm (ln) parameter means were calculated by transforming the ln means back to the linear scale (ie, geometric means).
†Ratio of test to reference parameter means for ln-transformed parameter (expressed as a percentage). Ln-transformed ratio was transformed back to linear scale.
‡The 90% CI for ratio of test to reference parameter means (expressed as a percentage). Ln-transformed confidence limits were transformed back to linear scale.

### Table IV. Tolerability of hydrocodone (per-protocol population).*

<table>
<thead>
<tr>
<th>Type of AE</th>
<th>Hydrocodone Bitartrate 20 mg + Paroxetine</th>
<th>Hydrocodone Bitartrate 20 mg + Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before Administration of Hydrocodone Bitartrate (n = 24)</td>
<td>After Administration of Hydrocodone Bitartrate (n = 23)</td>
</tr>
<tr>
<td>Any AE</td>
<td>7 (29)</td>
<td>4 (17)</td>
</tr>
<tr>
<td>Treatment-related AEs†</td>
<td>7 (29)</td>
<td>4 (17)</td>
</tr>
<tr>
<td>AEs occurring in &gt; 5% of subjects</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>4 (17)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Nausea</td>
<td>3 (13)</td>
<td>0</td>
</tr>
<tr>
<td>Asthenia</td>
<td>2 (8)</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>2 (8)</td>
<td>0</td>
</tr>
</tbody>
</table>

AE = adverse event.
*AEs are listed by Medical Dictionary for Regulatory Activities preferred terms as number of occurrences (%); all other data are listed as number of subjects (%). None of the AEs was considered moderate or severe in intensity. No deaths, serious AEs, or early discontinuations due to AEs were reported.
†Related to study medication = unlikely, possibly, probably, or definitely related categories on the AE case-report form.
lesser peak concentrations of hydromorphone after the administration of hydrocodone; however, CYP2D6-metabolizer status does not appear to affect the pharmacodynamic response to hydrocodone. Even with the abolishment of the CYP2D6 minor oxidative pathway of metabolism by quinidine in poor CYP2D6 metabolizers of hydrocodone, extensive as well as poor metabolizers responded similarly to oral hydrocodone. These data suggest only a small role of hydromorphone in eliciting abuse-related responses to oral hydrocodone. The apparent discrepancy between the in vitro binding affinity and in vivo equianalgesia of hydromorphone relative to hydrocodone most likely may be due to lesser bioavailability (due to extensive first-pass metabolism of hydromorphone) and poor relative penetration of hydromorphone into the central nervous system.

CONCLUSION
In this population of 24 healthy subjects, the coadministration of single-dose HYD with paroxetine at steady state did not alter systemic exposure to hydrocodone, suggesting that HYD can be coadministered with CYP2D6 inhibitors at therapeutic doses, without dosage modification.

ACKNOWLEDGMENTS
Editorial support was provided by Meryl Gersh, PhD, and Karen Stauffer, PhD, QSci Communications, LLC. All of the authors were involved in the study design and analysis and interpretation of the data, provided critical review of manuscript drafts, and approved the final version of the manuscript for submission.

CONFLICTS OF INTEREST
Purdue Pharma L.P. funded this study and editorial support, and was involved in the study design; the collection, analysis, and interpretation of the data; the writing of the manuscript; and the decision to submit the manuscript for publication.

Dr. Kapil, Ms. Friedman, Ms. Cipriano, and Drs. Shet and Harris are employees of Purdue Pharma L.P. Mr. Michels was an employee of Purdue Pharma L.P. at the time that the study was conducted and during the writing of the manuscript. Dr. Mondal is an employee of PPD, Inc, the contract research organization that conducted the study and was contracted by Purdue Pharma L.P. The authors have indicated that they have no other conflicts of interest with regard to the content of this article.

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