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Steady-State Pharmacokinetics of MNK-795, an Extended-Release Oxycodone and Acetaminophen Combination Analgesic: Results from 2 Active Comparator Studies

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Abstract

Two single-center, open-label, randomized, phase 1, multiple-dose studies (N=48 each) evaluated the steady-state pharmacokinetics and tolerability of MNK-795, a bilayer product with both immediate-release (IR) and extended-release (ER) components of oxycodone (OC) and acetaminophen (APAP; OC/APAP ER). Study 1 compared 1- and 2-tablet doses of OC/APAP ER (7.5 mg/325 mg; 15 mg/650 mg) administered every 12 hours and 1 tablet of IR OC/APAP (7.5 mg/325 mg) administered every 6 hours over 4.5 days. Study 2 compared OC/APAP ER administered as 2 tablets (15 mg/650 mg) every 12 hours with IR oxycodone (15 mg), IR tramadol/APAP (37.5 mg/325 mg), and IR OC/APAP (7.5 mg/325 mg), each administered as 1 tablet every 6 hours over 4.5 days. In both studies, steady-state, dose-normalized, $AUC_{0\text{-}12h}$, C_{avg}, and C_{min} for oxycodone were similar between OC/APAP ER and each comparator; however, the degree of fluctuation and swing in oxycodone concentrations were greater with the more frequently dosed IR formulations. Acetaminophen concentrations reached similar peak levels to the IR products, but with OC/APAP ER acetaminophen concentrations tapered to levels that were below those observed with the IR comparators by 7 hours after the last dose. The most commonly observed adverse events included nausea, vomiting, dizziness, and pruritus.

Keywords: Analgesic: Pain; Opioid; Extended-release; Oxycodone; Acetaminophen; Pharmacokinetics

Abbreviations: ANOVA: Analysis of Variance; AE: Adverse Event; APAP: Acetaminophen; AUC: Area under the Plasma Concentration-Time Curve; $AUC_{0\text{-}12h}$: AUC from time 0 to 12 hours; $AUC_{0\text{-}12ss}$: Steady-State AUC from Time 0 to 12 hours; C_{avgss}: Steady-State Average Observed Plasma Concentration During the Dosing Interval; C_{max}: Maximum plasma concentration; C_{maxss}: Steady-State C_{max}; C_{min}: Minimum Plasma Concentration; C_{minss}: Steady-State C_{min}; CI: Confidence Interval; DFL: Degree of Fluctuation; ECG: Electrocardiogram; ER: Extended-Release; IR=Immediate-Release; K_{el}: Apparent First-Order Terminal Elimination Rate Constant; LC-MS/MS: Liquid Chromatography–Tandem Mass Spectrometry; LS: Least Squares; OC=Oxycodone; PK: Pharmacokinetics; SAE=Serious Adverse Event; SD: Standard Deviation; Swing: Swing of Plasma Concentrations; $t_{1/2}$: Elimination Half-Life; t_{lag}: Lag time; T_{max}: Time to Peak Plasma Concentrations; T_{maxss}=Steady-State T_{max}

Introduction

Acute pain is common, affecting between 25 and 97 million Americans each year [1-5]. Although several analgesic options exist, acute pain is often undermanaged, and many patients continue to experience pain [5-7]. Opioids are commonly used to manage moderate to severe acute pain [6,8]. Oxycodone is a semisynthetic opioid used primarily for its analgesic effects [9], and has demonstrated high oral bioavailability and linear pharmacokinetics (PK) [10]. Immediate-release (IR) formulations of oxycodone have relatively short duration of action, requiring administration every 4 to 6 hours to maintain analgesia, whereas extended-release (ER) formulations are designed to maintain plasma concentrations for longer periods with less frequent dosing [10-12]. Opioids are often used in combination with acetaminophen, a nonopioid, nonsalicylate analgesic/antipyretic that is postulated to exert analgesic effects predominantly via central mechanisms [13,14].

The primary goal of combination therapy is to provide adequate analgesia while limiting side effects of both agents. Combining agents with complementary mechanisms of action, particularly those which are proposed to have additive analgesic effects, allow for lower doses of the individual agents, and thus, may result in a lower risk for concentration-dependent adverse events (AEs) [15-19]. Combination oxycodone/acetaminophen (OC/APAP) therapy with IR products has demonstrated clinical efficac across a variety of conditions associated with moderate to severe pain [14,15,20-28].

MNK-795 (OC/APAP ER) is a combination oxycodone and acetaminophen bilayer analgesic with both IR and ER components designed for 12-hour dosing. OC/APAP ER tablets employ a dual-layer biphasic delivery mechanism that, when administered as a single dose (ie, 2 tablets), is designed to deliver 3.75 mg OC/325 mg APAP through the IR component and 11.25 mg OC/325 mg APAP through the ER component, which releases medication at a steady rate in the upper gastrointestinal tract.

Immediate-release IR-OC/APAP (Percocet) was used initially as a comparator in Study 1. Since Percocet was not approved by the FDA under a New Drug Application (NDA), but rather an Abbreviated New Drug Application (ANDA), the pharmacokinetics of OC and APAP

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from MNK-795 (7.5 mg OC/325 mg APAP) were also compared to NDA approved immediate-release Roxicodone and Ultracet. In addition, given that the PK comparison between MNK-795 and the IR comparator was still highly relevant for prescribing physicians, Percocet 7.5 mg OC/325 mg APAP was included in this study.

We report results of 2 studies conducted in healthy volunteers to evaluate the steady-state PK of OC/APAP ER. The first study compared 1- and 2-tablet dosages of OC/APAP ER administered every 12 hours over 4.5 days with 1 tablet dosages of IR OC/APAP administered every 6 hours over 4.5 days. The second study compared OC/APAP ER administered as 2 tablets every 12 hours with IR OC, IR tramadol/APAP, and IR OC/APAP, each administered as 1 tablet every 6 hours.

Materials and Methods

Participants

Inclusion and exclusion criteria were similar in both studies. Healthy men or nonlactating, nonpregnant women, 18 to 55 years of age, with body mass index between 19 and ≤ 30 kg/m^2 and minimum weight of 130 lb were eligible. Exclusion criteria included smoking or use of nicotine-containing products in the previous 6 months; history of drug or alcohol use or positive urine test for drugs of abuse; use of prescription or over-the-counter medications within 14 days of study check-in; history of medication allergy, hypersensitivity, or intolerance of opioid products (including tramadol in study 2) or acetaminophen; history of any condition that may interfere with absorption, distribution, metabolism, or excretion of study medication; or previous gastric bypass or gastric band surgery. Participants with histories of abdominal and/or pelvic surgery within 1 year of study initiation; previous cardiothoracic surgery; histories of psychiatric symptoms or disorders requiring hospitalization, psychotherapy, and/or medication within 3 years of study initiation; acute or chronic gastrointestinal disease; histories of seizures or diagnosis of epilepsy or other seizure disorder or histories of conditions that might be specifically contraindicated or require caution while using oxycodone, acetaminophen, and/or tramadol were also excluded.

Ethical conduct

These studies were conducted in accordance with Good Clinical Practice guidelines, and the protocol was approved by the investigator's Institutional Review Board (IntegReview, Austin, TX, USA). Written informed consent was obtained from participants before enrollment.

Study design and treatments

Both studies were single-center, open-label, randomized, phase 1, multiple-dose trials. Study 1 was a 3-period, 6-sequence, crossover study. Participants received each of the following treatments for 4.5 days under fasted conditions: (1) OC/APAP ER (1 tablet; 7.5 mg/325 mg) taken every 12 hours (9 tablets total); (2) OC/APAP ER (2 tablets; total, 15 mg/650 mg) taken every 12 hours (18 tablets total); and (3) IR OC/APAP (1 tablet; 7.5 mg/325 mg) taken every 6 hours (18 tablets total). The study included a screening visit and 3 confinement periods of approximately 7 days each, with a minimum of 14 days between the start of each period, and a telephone follow-up of at least 7 days after study completion. Plasma samples for PK analysis were collected at intervals up to 144 hours after the first dose of each confinement period. AEs were monitored throughout each confinement period and during the 7-day follow-up.

Study 2 was a 4-period, 4-sequence study in which participants received each of the following treatments under fasted conditions for 4.5 days: (1) OC/APAP ER (2 tablets; total, 15 mg/650 mg) taken every 12 hours (18 tablets total); (2) IR oxycodone (1 tablet; 15 mg) taken every 6 hours (18 tablets total); (3) IR tramadol/APAP (1 tablet; 37.5 mg/325 mg) taken every 6 hours (18 tablets total); and (4) IR OC/APAP (1 tablet; 7.5 mg/325 mg) taken every 6 hours (18 tablets total). The study included a screening visit and 4 confinement periods of approximately 7 days each, and 3 intervals of at least 13 days between the start of each period. Plasma samples for PK analysis were collected at intervals up to 132 hours after the first dose of each confinement period. AEs were monitored from the time the informed consent form was signed through either the end of the study or upon early termination. Ongoing AEs were followed by the investigator until the events subsided, values returned to a normal range, follow-up was determined to be no longer necessary, or the participant was referred to his or her usual physician for follow-up.

Plasma sampling and assessments

Participants fasted overnight for a minimum of 10 hours before the first dose. A meal was provided approximately 4 hours postdose. In study 1, blood samples for PK analysis of oxycodone and acetaminophen were collected by venipuncture on day 1: predose, 15, 30, 45 minutes, and 1, 2, 3, 4, 6, 7, 8, 10, and 12 hours postdose, with additional samples collected at 15, 30, and 45 minutes after the 6-hour IR OC/APAP dose; days 2 to 4: before the morning dose (24, 48, and 72 h); and day 5 to 7: predose (before hour 96), then 15, 30, and 45 minutes after the dose at hour 96, and at 97, 98, 99, 100, 102, 103, 104, 106, 108, 112, 120 (day 6), 132, and 144 hours (day 7). Additional samples were collected 15, 30, and 45 minutes after the dose at 102 hours for IR OC/APAP. In study 2, blood samples for PK analysis of oxycodone and acetaminophen were collected by venipuncture before dosing and at 0.5, 1, 2, 3, 4, 6, 6.5 (IR formulations only), 8, and 12 hours after dosing on day 1; before the morning dose on days 2 through 4 (24, 48, and 72 h); before dosing on day 5 (96) and at 96.5, 97, 98, 99, 100, 102, 102.5 (IR formulations only), 104, 108, 120 h (day 6), and 132 hours. In both studies, blood samples were collected into pre-chilled vacuum collection tubes containing EDTA and placed into a cryoblock immediately after collection. Samples were centrifuged at approximately 4°C, and the plasma fraction was divided into 2 labeled polypropylene tubes and frozen until analysis using a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) assay at a bioanalytical laboratory (PPD, Inc., Middleton, Wisconsin, USA). The LC-MS/MS method for oxycodone was validated over a calibration range of 0.100 to 100 ng/mL, and the method for acetaminophen was validated over a calibration range of 100 to 50,000 ng/mL. Internal standards for the quantitative LC-MS/MS method were OC-d_6 and APAP-d_4. Human plasma containing oxycodone, acetaminophen, and the internal standards was extracted, reconstituted, and injected onto the LC-MS/MS. Each calibration curve was calculated using a linear-weighted least squares regression algorithm, and calibration curves were plotted as the peak area of the analyte to the internal standard versus concentration.

Oxycodone and acetaminophen pharmacokinetics were examined using the following parameters: day 1 - area under the plasma concentration-time curve (AUC) from time 0 to 12 hours ($AUC_{0\text{-}12h}$), maximum observed plasma concentration (C_{max}), minimum plasma concentration obtained at 12 hours after dosing (C_{min}), time to C_{max} (T_{max}), lag time (ie, time between administration and the first measurable concentration; t_{lag}); day 5 - steady-state AUC from time 0 to 12 hours

($AUC_{0\text{-}12hss}$), steady-state C_{max} (C_{maxss}), steady-state C_{min} (C_{minss}), steady-state average observed plasma concentration during the dosing interval (C_{avgss}), degree of fluctuation in plasma concentrations (DFL), swing of plasma concentrations (swing), steady-state T_{max} (T_{maxss}), apparent first order terminal elimination rate constant (K_{el}), and apparent plasma terminal elimination half-life ($t_{1/2}$). DFL and swing are parameters used to assess delivery properties of formulations at steady state. DFL was calculated as $(C_{maxss}–C_{minss}/C_{avgss})•100\%$, and swing was calculated as $(C_{maxss}–C_{minss})/C_{minss}$ [29].

Safety and tolerability were assessed by monitoring AEs and conducting clinical laboratory tests (eg, hematology, serum chemistry, and urinalysis), vital sign and pulse oximetry measurements, electrocardiograms (ECGs), physical examinations, and impaired judgment evaluations.

Statistics

Data from all-dosed subjects were used for the safety analyses. The completer population was defined as subjects who finished all study periods and was used for the steady-state PK analysis of OC/APAP ER. Descriptive statistics and frequency counts were used for subject disposition, demographics, and baseline characteristics. Summary statistics were compiled for treatment-emergent AEs. Actual values and changes from baseline were assessed by treatment laboratory measures, vital signs, pulse oximetry, and ECGs.

Individual plasma concentration versus actual time data were used to estimate the PK parameters for oxycodone and acetaminophen by standard noncompartmental methods using Phoenix® WinNonlin® (Pharsight Corporation, St. Louis, Missouri, USA) Version 6.1 for each individual in each treatment. PK parameters were summarized by treatment using descriptive statistics, number of subjects, mean, standard deviation (SD), median, minimum, and maximum. Statistical comparisons between conditions at steady-state (day 5) were made for dose-normalized (plasma concentration ÷ dose administered) PK parameters of C_{maxss}, C_{minss}, C_{avgss}, and $AUC_{0\text{-}12ss}$, and natural log transformed PK parameters $AUC_{0\text{-}12hss}$, C_{maxss}, C_{avgss}, C_{minss} of DFL and swing, using analysis of variance (ANOVA) with PK parameters defined as dependent variables with sequence, treatment, and period as fixed effects, and subjects nested within sequences as random effects. Comparisons were based on geometric least squares (LS) means, percentage ratio of geometric LS means, and corresponding 90% confidence intervals (CI). A 90% CI of geometric LS means ratios fully contained within 80% to 125% concluded that there was no difference between treatments.

Non-transformed PK parameters (K_{el} and $t_{1/2}$) were compared with ANOVA using these PK parameters as the dependent variable, sequence, treatment, and period as fixed effects, and subjects nested within sequences as random effects. LS means, difference of the LS means, 90% CI of the difference, and *P* values for testing fixed effects were calculated. Wilcoxon signed rank tests were used to determine statistical significance of median difference for T_{max} at steady-state between treatments at a significance level of $P \leq 0.05$.

In addition, an analysis of the time that steady-state concentrations were reached was performed using ANOVA with the natural log-transformed PK parameter C_{min} defined as the dependent variable, day and sequence as fixed effects, and subjects nested within sequence as random effects. Helmert transformation compared geometric mean concentration of the corresponding study day to the geometric mean concentration pooled over all remaining days within treatment. Comparisons continued until the day the comparison was not statistically significant (ie, α=0.05). The earliest study day that included a nonsignificant contrast was considered as the study day on which steady-state concentrations were attained. Geometric LS means, percentage ratio of geometric LS means, and corresponding 90% CI of the ratio were calculated. All analyses were performed using SAS® software (SAS Institute, Inc., Cary, North Carolina, USA), version 9.1

Results

Participants

Forty-eight healthy subjects were enrolled in each study and received at least 1 dose of treatment. In study 1, 33 subjects (69%) completed all 3 treatment periods. Fifteen subjects withdrew from the study: 10 (21%) due to the AE of vomiting (per protocol), 1 (2%) each due to anemia and streptococcal pharyngitis, and 3 (6%) because of a family emergency. In study 2, 24 subjects (50%) completed all 4 treatment periods. Twenty-four subjects withdrew from the study: 22 (46%) due to vomiting (per protocol), 1 (2%) because withdrawal criteria were met (positive urinary drug screen at check-in), and 1 (2%) of these subjects did not respond to attempts to follow-up on the resolution of AEs. Table 1 presents demographics and baseline characteristics of all dosed subjects in both studies.

Oxycodone Pharmacokinetics: Table 2 presents estimates of the oxycodone PK parameters on day 1 and day 5 at steady state.

Day 1: In both studies, no lag ($t_{lag=}0$) was observed between the first dose administration of any treatment on day 1 and the detection of oxycodone in plasma. Day 1 mean oxycodone $AUC_{0\text{-}12h}$ and C_{max} increased proportionally with 1- and 2-tablet doses of OC/APAP ER. In study 1, mean oxycodone $AUC_{0\text{-}12h}$ was similar for the 2-tablet dose of OC/APAP ER and an equivalent dose (administered as 7.5 mg/325 mg q6h for a total of 15 mg/650 mg over a 12-hour period) of IR OC/APAP, whereas C_{max} was higher for IR OC/APAP. In study 2, oxycodone $AUC_{0\text{-}12h}$ and C_{max} were similar for equivalent doses of OC/APAP ER (15 mg/650 mg) administered every 12 hours and IR OC/

	Study 1	Study 2
Characteristic	**All Dosed Subjects (N=48)**	**All Dosed Subjects (N=48)**
Age, y		
Mean (SD)	32.1 (10.1)	31.1 (9.13)
Range	18-51	18-51
Sex, n (%)		
Male	24 (50.0)	27 (56.3)
Female	24 (50.0)	21 (43.8)
Race, n (%)		
White	32 (66.7)	33 (68.8)
Black or African American	14 (29.2)	15 (31.3)
Asian	1 (2.1)	---
Multiracial	1 (2.1)	---
Ethnicity, n (%)		
Hispanic or Latino	18 (37.5)	22 (45.8)
Not Hispanic or Latino	30 (62.5)	26 (54.2)
Weight, kg, mean (SD)	73.0 (9.9)	72.9 (8.0)
Body mass index, kg/m^2		
Mean (SD)	25.7 (2.6)	25.5 (2.6)
Range	20.6–29.8	19.6–29.8

Table 1: Demographics and baseline characteristics.

	Study 1 (n=33)			Study 2 (n=24)		
Parameter, mean (SD)	**OC/APAP ER 1 tablet q12h**	**OC/APAP ER 2 tablets q12h**	**IR OC/APAP 1 tablet q6h**	**OC/APAP ER 2 tablets q12h**	**IR Oxycodone 1 tablet q6h**	**IR OC/APAP 1 tablet q6h**
Day 1						
AUC_{0-12h}, ng•h/mL	66.9 (15.1)	135.9 (30.8)	141.7 (29.8)	136.1 (23.7)	242.6 (19.9)	132.5 (22.8)
C_{max}, ng/mL	8.34 (2.37)	17.05 (3.97)	21.93 (4.80)	16.04 (3.64)	34.78 (8.64)	19.83 (5.07)
T_{max}, h[a]	3.0 (0.75-7.0)	3.0 (0.5-5.9)	7.0 (0.5-8.0)	3.0 (0.5-8.0)	7.0 (0.75-10.0)	8.0 (0.5-10.0)
t_{lag}, h[a]	0.0 (0.0-0.5)	0.0 (0.0-0.3)	0.0 (0.0-0.25)	0.0 (0.0-0.27)	0.0 (0.0-0.25)	0.0 (0.0-0.25)
Day 5 (steady state)						
$AUC_{0-12hss}$, ng•h/mL	102.4 (29.3)	208.6 (59.3)	208.9 (57.3)	208.3 (45.3)	376.9 (83.9)	191.5 (42.8)
C_{avgss}, ng/mL	8.53 (2.44)	17.38 (4.94)	17.41 (4.78)	17.36 (3.78)	31.41 (6.99)	15.96 (3.57)
C_{maxss}, ng/mL	12.67 (3.48)[b]	25.67 (7.49)[b]	30.50 (8.91)	24.00 (5.38)	45.15 (10.54)	26.32 (6.18)
C_{minss}, ng/mL	4.06 (1.40)	8.98 (3.52)	8.78 (3.17)	9.31 (2.39)	19.91 (4.93)	8.81 (2.40)
Degree of fluctuation, %	101.7 (14.1)[b]	97.2 (18.8)[b]	126.8 (27.9)	83.9 (17.6)[b]	79.9 (19.8)	110.9 (33.4)
Swing	2.2 (0.6)[b]	2.0 (0.7)[b]	2.7 (0.9)	1.7 (0.6)[b]	1.3 (0.5)	2.1 (0.9)
T_{maxss}, h[a]	2.0 (0.5-10.0)[b]	2.0 (0.5-7.0)[b]	6.5 (0.5-8.0)	3.0 (1.0, 5.9)[b,c]	3.0 (1.0, 12.0)	7.3 (0.5, 8.1)
$t_{½}$, h	5.5 (1.2)	6.1 (1.5)[b]	5.5 (1.7)	5.4 (0.9)[b,c]	4.6 (0.6)	4.7 (0.6)
K_{el}, 1/h	0.1326 (0.0269)	0.1199 (0.0291)[b]	1.1387 (0.0418)	0.1318 (0.0223)[b,c]	0.1525 (0.0206)	0.1517 (0.0205)

[a]Median (range); [b]Reached statistical significance vs IR OC/APAP; [c]Reached statistical significance vs IR oxycodone
APAP, acetaminophen; $AUC_{0-12hss}$, area under the plasma concentration-time curve from time 0 to 12 h at steady state; C_{avgss}, average observed plasma concentration during the dosing interval at steady state; C_{maxss}, maximum observed plasma concentration at steady state; C_{minss}, plasma concentration obtained at predose during steady state; ER, extended release; IR, immediate release; K_{el}, apparent terminal elimination rate constant; OC, oxycodone; T_{maxss}, time to C_{max} at steady state; $t_{½}$, terminal elimination half-life

Table 2: Day 1 and steady-state (day 5) pharmacokinetic estimates for oxycodone.

APAP (7.5 mg/325 mg) administered every 6 hours and lower for OC/APAP ER (15 mg/650 mg) administered every 12 hours compared with IR oxycodone (15 mg) administered every 6 hours (30 mg OC over a 12-hour period; Table 2). In both studies, oxycodone T_{max} was 3 hours after the first administration of OC/APAP E

Steady-State (Day 5): In study 1, steady-state oxycodone plasma concentrations were achieved on day 4 (P=0.774) and day 3 (P=0.267) for the 1- and 2-tablet doses of OC/APAP ER, respectively, whereas steady-state was not attained for IR OC/APAP (P<0.05). For the 2-tablet dose of OC/APAP ER, C_{min} was above 10 ng/mL on each day in study 1. In study 2, steady-state oxycodone concentrations were attained within 24 hours after initial administration of OC/APAP ER (P=0.138) and IR OC/APAP (P=0.144). Figure 1A (study 1) and 1B (study 2) present steady-state plasma oxycodone concentrations after the final dose of OC/APAP ER on day 5. At steady-state, mean oxycodone plasma concentrations increased rapidly after administration of OC/APAP ER and were sustained throughout the dosing interval. Oxycodone plasma concentrations were approximately 37% of peak levels by 12 hours after dosing and remained detectable in plasma for more than 24 hours after the final dose in study 2

In study 1, the 90% CIs of the geometric LS means ratios for steady-state (day 5) dose normalized oxycodone PK assessments were within the no difference range for the comparison between the 1- and 2-tablet doses of OC/APAP ER for $AUC_{0-12hss}$, C_{maxss}, C_{minss}, C_{avgss}, and DFL, indicating dose proportionality with respect to oxycodone exposure. In addition, the 90% CIs for $AUC_{0-12hss}$, C_{minss}, and C_{avgss} were completely within the no difference range (80%-125%) for the comparison between both doses OC/APAP ER and IR OC/APAP, indicating similar overall oxycodone bioavailability between these treatments at steady-state. The findings in study 2 also showed similar oxycodone bioavailability for dose-normalized OC/APAP ER, IR OC/APAP, and IR oxycodone at steady-state, as demonstrated by the 90% CIs of the geometric LS means ratios being fully contained within the range of 80% to 125% for oxycodone $AUC_{0-12hss}$, C_{maxss}, C_{avgss}, and C_{minss}. In study 1 (Day 5), intrasubject variability (CV) was about 11% for $AUC_{0-12\ hss}$, 15% for C_{maxss}, and 18% for C_{minss}, respectively, following administration of 1 or 2 OC/APAP ER tablets. Intersubject variability (CV) for both $AUC_{0-12\ hss}$ and C_{maxss} was about 28% and, ranged from 35% to 39% for C_{minss}, respectively, for oxycodone following administration of 1 or 2 tablets of OC/APAP ER. Following multiple doses of 2 tablets of OC/APAP ER in study 2 (Day 5), intrasubject variability was 12% for $AUC_{0-12\ hss}$ and 18% for both C_{maxss}, and C_{minss}, respectively. Intersubject variability was 22% for both $AUC_{0-12\ hss}$ and C_{maxss} and was 26% for C_{minss}, respectively.

PK variables that did demonstrate significant differences in study 1 included C_{maxss}, swing, and DFL, which were 17%, 15%, and 19% lower with the 1-tablet dose and 16%, 24%, and 23% lower with the 2-tablet dose, respectively, compared with IR OC/APAP. The LS means ratios (90% CI) for C_{maxss}, swing, and DFL between OC/APAP ER (1 tablet) and IR OC/APAP were 82.9% (77.8%-88.2%), 81.5% (76.0%-87.3%), and 85.3% (75.7%-96.1%), respectively; and between OC/APAP ER (2 tablets) and IR OC/APAP were 83.7% (78.6%-89.1%), 75.6% (67.1%-85.2%), and 76.9% (71.7%-82.5%), respectively. T_{maxss} was similar between the 1- and 2-tablet doses of OC/APAP ER, but significantly shorter than IR OC/APAP and IR oxycodone administered every 6 hours (P<0.05) as maximum concentrations of these IR products occurred after the second dose on Day 5 (Table 2). For 2-tablets of OC/APAP ER, the $t_{1/2}$ of oxycodone was significantly longer and K_{el} was significantly slower than for IR OC/APAP P<0.05).

For study 2, DFL of oxycodone concentrations with OC/APAP ER during the 12-hour dosing interval was similar to IR oxycodone administered every 6 hours but 23% less than that from IR OC/APAP administered every 6 hours (77.3%: 90% CI, 69.3%-86.3%). Swing in oxycodone concentrations for OC/APAP ER was also statistically smaller than IR OC/APAP (80.0%: 90% CI, 67.6%-94.6%). LS mean T_{maxss} was significantly shorter for OC/APAP ER than IR OC/APAP and IR oxycodone administered every 6 hours (P<0.05), which were observed after the second dose on day 5. The $t_{1/2}$ of oxycodone from OC/APAP ER (5.5 h) was approximately 1 hour longer than that from IR oxycodone (4.7 h) or IR OC/APAP (4.6 h; P<.001 for both).

Acetaminophen Pharmacokinetics: Table 3 presents estimates of the acetaminophen PK parameters on day 1 and day 5 at steady state.

Day 1: In both studies there was also no lag in the appearance of acetaminophen in plasma following the administration of any treatment on day 1. Acetaminophen T_{max} was reached within 1 hour for each treatment in both studies with the exception of IR tramadol/APAP in study 2, in which acetaminophen T_{max} was reached at 0.75 hours after the second dose. In study 1, mean acetaminophen $AUC_{0\text{-}12h}$ and C_{max} were proportional with the 1- and 2-tablet doses of OC/APAP ER. In addition, acetaminophen $AUC_{0\text{-}12h}$ and C_{max} for IR OC/APAP were similar to that of the 2-tablet dose of OC/APAP ER. In study 2, mean day 1 acetaminophen $AUC_{0\text{-}12h}$ and C_{max} were comparable between all 3 treatments (Table 3).

Steady-State (Day 5): In study 1, steady-state acetaminophen concentrations were achieved on day 4 for the 1-tablet dose (P=0.787) of OC/APAP ER and on day 2 for the 2-tablet dose (P=0.188) of OC/APAP ER and IR OC/APAP (P=0.675). Steady-state acetaminophen concentrations in study 2 were reached within 24 hours after initial administration of OC/APAP ER (P=0.089) and IR tramadol/APAP (P=0.959), and within 12 hours for IR OC/APAP (P=0.052). In addition, C_{min} values for both doses of OC/APAP ER were below those for each comparator in both studies. Figure 2A (study 1) and 2B (study 2) present steady-state acetaminophen plasma concentrations after the final dose of OC/APAP ER on day 5

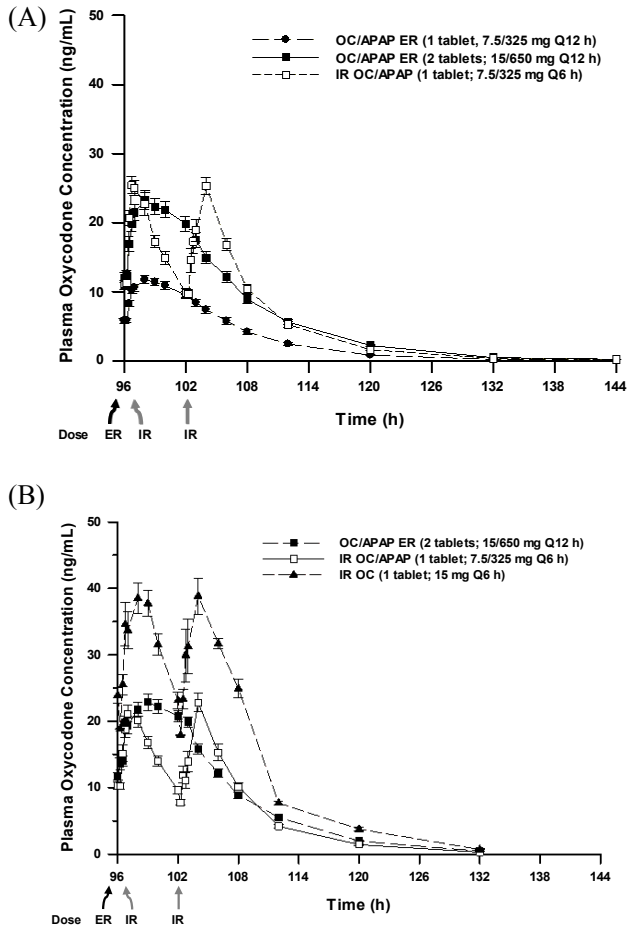

Figure 1: A. Mean (SE) steady-state plasma concentration of oxycodone after the last dose of OC/APAP ER in study 1. **B.** Mean (SE) steady-state plasma concentration of oxycodone after the last dose of OC/APAP ER in study 2 (B). Arrows indicate timing of doses.

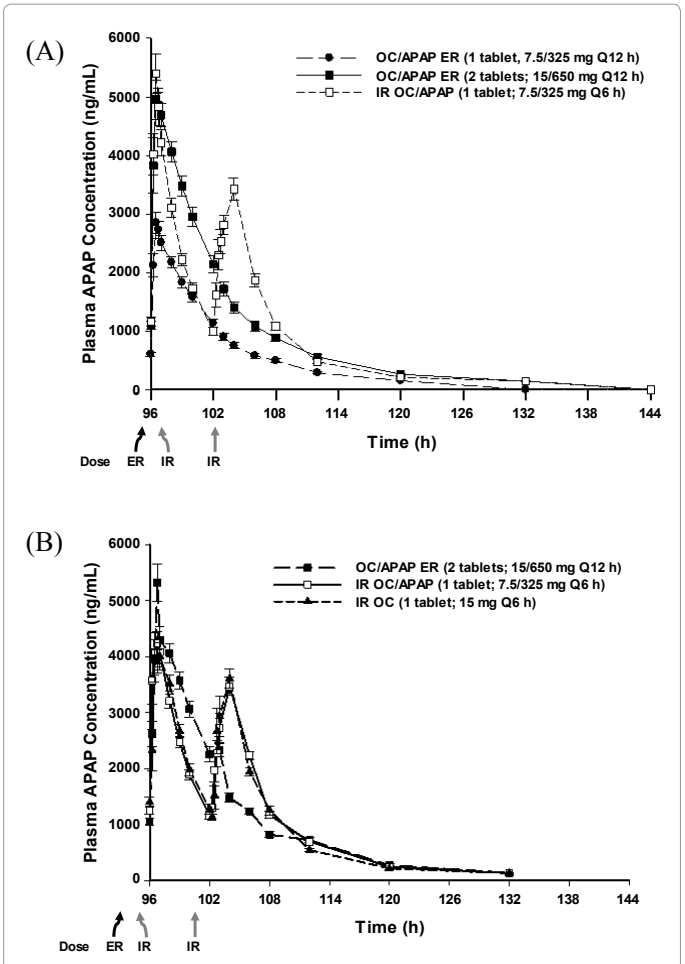

Figure 2: A. Mean (SE) steady-state plasma concentration of acetaminophen after the last dose of OC/APAP ER in study 1. **B.** Mean (SE) steady-state plasma concentration of acetaminophen after the last dose of OC/APAP ER in study 2 (B).

In both studies, acetaminophen T_{maxss} was reached within 1 hour after administration of each study medication (Table 3). At steady-state (day 5), mean acetaminophen plasma concentrations from OC/APAP ER increased rapidly after administration and declined to levels below those of the comparators by 7 to 12 hours after the initial dose on day 5. In study 1, the comparisons of geometric LS means ratios for the results for dose-normalized acetaminophen $AUC_{0\text{-}12hss}$, C_{maxss}, C_{minss}, C_{avgss}, DFL, and swing found no differences between OC/APAP ER and the comparators from each study, as indicated by the 90% CIs being within the no difference range. However, in study 2, acetaminophen C_{minss} after administration of OC/APAP ER was 21% lower than that observed after IR tramadol/APAP and 22% lower than after IR OC/APAP (LS means ratios [90% CI] of 79.1% [73.4%-85.4%] and 78.4% [72.8%-84.5%], respectively). In addition, swing in acetaminophen plasma concentrations was higher for higher for OC/APAP ER than for tramadol/APAP and IR OC/APAP, with LS means ratios (90% CI) of 127.6% (106.1%-153.5%) and 132.6% (110.5%-159.3%). In study 1, acetaminophen $t_{1/2}$ was longer for the 2-tablet dose of OC/APAP ER

compared with IR OC/APAP (P<0.05). In study 2, acetaminophen T_{max} were not significantly different between treatments (P>0.05), and acetaminophen $t_{1/2}$ for OC/APAP ER were similar to those for IR OC/APAP; however, the least squares mean of $t_{1/2}$ was approximately 2.3 hours longer for OC/APAP ER than for IR tramadol/APAP (P<0.05).

Across studies, intrasubject variability (CV) for acetaminophen was 9% for $AUC_{0\text{-}12\ hss}$, ranged from 19% to 23% for C_{maxss} and was 15% for C_{minss}, respectively, following administration of 1 or 2 OC/APAP ER tablets. Intersubject variability (CV) for acetaminophen ranged from 21% to 27% for $AUC_{0\text{-}12\ hss}$, 24% to 33% for C_{maxss} and 32% to 39% for C_{minss}, respectively, after administration of 1 or 2 tablets of OC/APAP ER.

Overall, these findings suggest that acetaminophen exposure was proportional to the administered doses of OC/APAP ER, while producing similar steady-state acetaminophen bioavailability for OC/APAP ER versus IR OC/APAP and IR tramadol/APAP.

Safety/Tolerability

Table 4 presents AEs for each treatment condition in both studies. Overall in study 1, 42 of 48 subjects (87.5%) experienced ≥ 1 AE during any condition; 19 participants (47.5%) experienced an AE while receiving 1 tablet of OC/APAP ER, 29 participants (70.7%) with 2 tablets of OC/APAP ER, and 30 (73.2%) after receiving IR OC/APAP (Table 4). No serious AEs (SAEs) were reported during the study. The most common AEs overall were nausea (45.8%), pruritus (37.5%), headache (33.3%), dizziness (31.3%), infrequent bowel movements (20.8%), vomiting (20.8%), and somnolence (16.7%). In general, OC/APAP ER administered as 1 tablet had fewer AEs than either 2 tablets of OC/APAP ER or IR OC/APAP. No significant clinical differences in safety or tolerability were reported between OC/APAP ER (2 tablets) and IR OC/APAP. Somnolence was numerically greater for both doses of OC/APAP ER compared with IR OC/APAP. Ten participants (21%) discontinued because of vomiting per protocol specification; 1 during

	Study 1 (n=33)			Study 2 (n=24)		
Parameter, mean (SD)	**OC/APAP ER 1 tablet q12h**	**OC/APAP ER 2 tablets q12h**	**IR OC/APAP 1 tablet q6h**	**OC/APAP ER 2 tablets q12h**	**IR tramadol/APAP 1 tablet q6h**	**IR OC/APAP 1 tablet q6h**
Day 1						
$AUC_{0\text{-}12h}$, ng•h/mL	12192 (3331)	24141 (6436)	24884 (6656)	24924 (5667)	26343 (4721)	25094 (5085)
C_{max}, ng/mL	2631 (815)	5245 (1473)	5146 (1553)	4858 (1066)	4568 (976)	4318 (1006)
T_{max}, h[a]	0.55 (0.25-3.0)	0.75 (0.25-2.0)	0.50 (0.25-8.0)	1.0 (0.5-4.0)	6.75 (0.5-8.2)	0.53 (0.5-8.0)
t_{lag}, h[a]	0.0 (0.0-0.25)	0.0 (0.0-0.25)	0.0 (0.0-0.0)	0.0 (0.0-0.0)	0.0 (0.0-0.3)	0.0 (0.0-0.0)
Day 5 (steady state)						
$AUC_{0\text{-}12hss}$, ng•h/mL	15307 (4092)	28512 (7714)	28719 (7023)	28160.40 (5807.09)	29711.92 (5427.37)	29284.22 (5477.73)
C_{avgss}, ng/mL	1276 (341)	2376 (643)	2393 (585)	2346.70 (483.92)	2475.99 (452.28)	2440.35 (456.48)
C_{maxss}, ng/mL	3117 (840)	5872 (1932)	5968 (1639)	4792.50 (1132.40)	5078.33 (1189.70)	4876.67 (1383.08)
C_{minss}, ng/mL	474.67 (163)	870.42 (336)	922.58 (321)	852.75 (273.25)[b,c]	1070.92 (367.35)	1069.13 (291.83)
Degree of fluctuation, %	212.1 (52.3)	218.1 (81.1)	213.8 (50.5)	169.1 (39.8)	163.9 (47.2)	155.3 (38.8)
Swing	6.0 (2.0)	6.6 (3.6)	5.9 (2.2)	5.1 (2.1)[b,c]	4.2 (2.1)	3.8 (1.6)
T_{maxss}, h[a]	0.5 (0.3-3.0)	0.5 (0.3-3.0)	0.5 (0.3-8.0)	1.0 (0.5, 4.0)	0.9 (0.3, 8.0)	0.8 (0.3, 8.0)
$t_{½}$, h	5.6 (1.4)	7.5 (2.9)[b]	5.7 (3.0)	6.9 (1.8)[c]	5.3 (1.1)	6.2 (1.8)
K_{el}, 1/h	0.1308 (0.0317)	0.1026 (0.0292)[b]	0.1416 (0.0515)	0.1072 (0.0285)[c]	0.1355 (0.0279)	0.1201 (0.0338)

[a]Median (range); [b]Reached statistical significance vs IR OC/APAP; [c]Reached statistical significance vs IR tramadol/APAP
APAP, acetaminophen; $AUC_{0\text{-}12hss}$, area under the plasma concentration-time curve from time 0 to 12 h at steady state; C_{avgss}, average observed plasma concentration during the dosing interval at steady state; C_{maxss}, maximum observed plasma concentration at steady state; C_{minss}, plasma concentration obtained at predose during steady state; ER, extended release; IR, immediate release; K_{el}, apparent terminal elimination rate constant; OC, oxycodone; T_{maxss}, time to C_{max} at steady state; $t_{½}$, terminal elimination half-life

Table 3: Day 1 and steady-state (day 5) pharmacokinetic estimates for acetaminophen.

	Study 1			Study 2			
AE, n (%)	**OC/APAP ER 1 tablet q12h (n=40)**	**OC/APAP ER 2 tablets q12h (n=41)**	**IR OC/APAP 1 tablet q6h (n=41)**	**OC/APAP ER 2 tablets q12h (n=33)**	**IR Oxycodone 1 tablet q6h (n=34)**	**IR tramadol/APAP 1 tablet q6h (n=28)**	**IR OC/APAP 1 tablet q6h (n=31)**
Subjects with at least 1 TEAE	19 (47.5)	29 (70.7)	30 (73.2)	15 (45.5)	28 (82.4)	12 (42.9)	20 (64.5)
Nausea	5 (12.5)	12 (29.3)	13 (31.7)	8 (24.2)	13 (38.2)	2 (7.1)	9 (29.0)
Vomiting	1 (2.5)	5 (12.2)	4 (9.8)	7 (21.2)	8 (23.5)	2 (7.1)	5 (16.1)
Dizziness	5 (12.5)	6 (14.6)	7 (17.1)	4 (12.1)	13 (38.2)	2 (7.1)	4 (12.9)
Pruritus	5 (12.5)	10 (24.4)	10 (24.4)	7 (21.2)	13 (38.2)	5 (17.9)	2 (6.5)
Headache	9 (22.5)	4 (9.8)	7 (17.1)	5 (15.2)	5 (14.7)	3 (10.7)	3 (9.7)
Feeling hot	0	1 (2.4)	3 (7.3)	2 (6.1)	4 (11.8)	1 (3.6)	2 (6.5)
Infrequent bowel movements	4 (10.0)	5 (12.2)	3 (7.3)	0 (0.0)	6 (17.6)	1 (3.6)	2 (6.5)
Abdominal pain	1 (2.5)	3 (7.3)	1 (2.4)	2 (6.1)	0 (0.0)	1 (3.6)	3 (9.7)
Somnolence	5 (12.5)	5 (12.2)	1 (2.4)	1 (3.0)	1 (2.9)	2 (7.1)	1 (3.2)

[a]AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA®; MedDRA MSSO, McLean, Virginia, USA)
APAP, acetaminophen; ER, extended release; IR, immediate release; OC, oxycodone; q6h, every 6 hours; q12h, every 12 hours; TEAE, treatment-emergent adverse event

Table 4: Summary of treatment-emergent adverse events[a].

1-tablet OC/APAP ER (7.5/325 mg q12h), 5 during 2-tablet OC/APAP ER (15/650 mg q12h), and 4 during 1-tablet IR OC/APAP (7.5/325 mg q6h).

In study 2, 44 of 48 subjects (91.7%) experienced ≥1 AE. More subjects reported AEs during IR oxycodone administration (82.4%) than during administration of IR OC/APAP (64.5%), OC/APAP ER (45.5%), or IR tramadol/APAP (42.9%) (Table 4). The most common AEs overall were nausea (54.2%), vomiting (45.8%), pruritus (39.6%), dizziness (39.6%), and headache (29.2%). As would be expected, AEs that are common to opioids (eg, nausea, vomiting, and dizziness) were low with IR tramadol/APAP and highest with the highest dose of oxycodone (ie, IR oxycodone 15 mg q6h). AEs were similar between OC/APAP ER (15/650 mg q12h) and IR OC/APAP (7.5/325 mg q6h). No SAEs were reported during the study. Twenty-two subjects (45.8%) were withdrawn from the study because of vomiting per protocol requirement, 7 (21.2%) of which occurred during OC/APAP ER treatment.

No apparent clinically significant treatment-related trends in vital sign and pulse oximetry measurements, ECG or physical examination findings were observed in either study. In study 1, one subject experienced an AE of anemia (during IR OC/APAP), which was accompanied by clinically significant decreases in erythrocytes, hemoglobin, and hematocrit on laboratory assessments. This AE was considered by the investigator to be mild and not related to study medication, and resolved after study discontinuation. In study 2, two participants had laboratory abnormalities that were considered by the investigator to be clinically significant. One subject experienced increased hepatic enzymes (alanine aminotransferase, 227 IU/L; aspartate aminotransferase, 142 IU/L; and gamma-glutamyl transferase, 90 IU/L) on day 7 with IR oxycodone, which returned to within the normal range at admission on the next treatment period. These elevations were considered by the investigator to be mild and possibly related to study medication. A second subject had a clinically significant urinalysis result of trichomoniasis during IR tramadol/APAP, which was considered by the investigator to be mild and not related to study medication. This participant was referred to his or her primary care physician for follow-up. No other clinically significant changes in laboratory measures were noted in either study.

Discussion

These multiple-dose PK studies show that administering OC/APAP ER every 12 hours resulted in plasma concentrations of oxycodone and acetaminophen comparable to that of the IR formulations administered every 6 hours. In study 1, steady-state levels of oxycodone and acetaminophen were attained within 2 to 4 days of dosing of OC/APAP ER, 1- and 2-tablet doses of OC/APAP ER demonstrated dose proportionality, and the relative bioavailabilities of oxycodone and acetaminophen following administration of 1 or 2 tablets of OC/APAP ER every 12 hours were comparable with that IR OC/APAP (dose normalized) administered every 6 hours. In addition, this study demonstrated lower peak oxycodone concentrations and less fluctuation in oxycodone concentrations with OC/APAP ER (administered q12h) compared with IR OC/APAP (administered q6h). In study 2, steady-state plasma concentrations of oxycodone and acetaminophen were achieved within 24 hours after initial administration of OC/APAP ER. Under steady-state conditions, overall bioavailability of oxycodone and acetaminophen with OC/APAP ER administered q12h was similar to that of the IR products administered q6h; however, less fluctuation in oxycodone plasma concentrations occurred with OC/APAP ER compared with IR OC/APAP.

Both studies also showed that after dosing OC/APAP ER, plasma levels of oxycodone and acetaminophen rose quickly with no lag in appearance, and oxycodone concentrations decreased more slowly than acetaminophen concentrations. After the last dose during steady state, acetaminophen plasma levels tapered off to levels below IR comparators approximately 7 to 12 hours after the last dose of OC/APAP ER. In two separate single-dose studies that fully characterized plasma concentration-time data for oxycodone and APAP, administration of OC/APAP ER showed similar results (K. Devarakonda, PhD, et al., J. Bioequivalence & Bioavailability, 2014 (In Press)). In addition to the tapering of acetaminophen concentrations after the final dose, in study 2, steady-state trough acetaminophen plasma concentrations after OC/APAP ER were 21% lower than after IR tramadol/APAP and 22% lower than after IR OC/APAP, suggesting a low level of acetaminophen prior to the next dose of OC/APAP ER. This effect is a function of the acetaminophen release characteristics of OC/APAP ER. In addition, OC/APAP ER tablets contain 325 mg of acetaminophen, and when administered as 2 tablets every 12 hours, the total amount of acetaminophen (1300 mg) remains below the daily dose limit recommended by the US Food and Drug Administration [30].

In these 2 cross-over studies, following administration of 1 or 2 tablets of OC/APAP ER the intrasubject variability (within subject) in $AUC_{0\text{-}12\ hss}$, C_{maxss}, and C_{minss} remained low for both oxycodone and APAP. Similarly, intersubject variability (across subjects) for AUC0-12 hss and C_{maxss} remained low. However, the overall minimum plasma concentration (C_{minss}) for oxycodone and APAP in both studies was relatively higher (range 32% to 39%) with the exception of C_{minss} for Study 2 that was 20% to 39% lower than in Study 1. This difference may be attributed to the variability in actual blood draw times prior to the 96 h timepoint in Study 1.

In these PK studies, OC/APAP ER provided consistent plasma levels with twice-daily (every 12 hours) administration. Multiple OC/APAP ER doses were generally well tolerated in healthy adult participants and, although the study population was small, no SAEs occurred. AEs occurring after administration of OC/APAP ER were similar to those occurring after administration of IR OC/APAP and IR tramadol/APAP and less frequent than after administration of IR OC. In both studies, the most common AEs affected the gastrointestinal and central nervous systems, consistent with those reported with opioid analgesics [6,31].

As typical with PK studies, the generalizability of these results is limited by the population enrolled (healthy volunteers) and the small sample size. In addition, using agents in a controlled clinical trial setting may not be representative of real-world dosing, particularly due to high medication adherence, rigidly timed administration, and continuous AE monitoring.

Conclusions

In conclusion, these multiple-dose PK studies demonstrated that at steady-state, 12-hour dosing of OC/APAP ER yielded plasma concentrations comparable to those of IR products administered every 6 hours, but with less fluctuation in plasma levels of oxycodone and lower trough plasma concentrations of acetaminophen. In addition, OC/APAP ER demonstrated dose proportionality between 1-tablet

and 2-tablet administrations. The adverse events occurring in this study were as would be expected for this class of medication and type of study.

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