Journal of
Bioequivalence & Bioavailability
ISSN: 0975-0851

Devarakonda et al., J Bioequiv Availab 2014, 6:2
DOI: 10.4172/jbb.1000178

Research Article Open Access

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

Krishna Devarakonda*, Terri Morton, Michael Giuliani, Kenneth Kostenbader and Thomas Barrett

Mallinckrodt Inc., 675 James McDonnell Blvd 302-3-W, Hazelwood, MO 63042, USA

Abstract

MNK-795, a combination oxycodone (OC) and acetaminophen (APAP) analgesic (OC/APAP ER), is a bilayer product with immediate-release (IR) and extended-release (ER) properties. Two single-center, open-label, randomized, phase 1, crossover studies were conducted in healthy participants (N=48 for each trial) to characterize the pharmacokinetics (PK) and bioavailability of OC/APAP ER. Study 1 compared the single-dose PK and bioavailability following administration of 1 or 2 tablets of OC/APAP ER with an IR OC/APAP formulation. Study 2 assessed the single-dose PK and bioavailability of 2 tablets of OC/APAP ER compared with those of marketed forms of IR oxycodone, IR tramadol/APAP, and IR OC/APAP. Safety and tolerability were monitored. In both studies, OC/APAP ER demonstrated a bimodal OC release pattern, with a rapid rise and no lag in plasma concentrations after dosing, followed by an ER period with concentrations peaking 3 to 4 hours postdose and extending over 12 hours. Acetaminophen concentrations also demonstrated an initial rapid rise but tapered off at 7 to 12 hours postdose. Bioavailability and overall exposure of oxycodone and acetaminophen were comparable between single doses of OC/APAP ER and IR comparators (2 doses, 6 hours apart). Adverse events were consistent with those seen with opioids.

Keywords: Analgesics; Oxycodone; Acetaminophen; Controlled-release; Pain; Opioids

Abbreviations: ANOVA: Analysis of Variance; AE: Adverse Event; APAP: Acetaminophen; $AUC_{0\text{-}inf}$: Area under the Plasma Concentration-Time Curve from Time 0 to Infinity; $AUC_{0\text{-}t}$: Area under the Plasma Concentration-Time Curve from Time 0 to the Last Quantifiable Concentration; C_{max}: Maximum Plasma Concentration; CI: Confidence Interval; 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; $t_{1/2}$: Elimination Half-Life; t_{lag}: Lag Time; T_{max}: Time to Peak Plasma Concentrations

Introduction

Opioid/acetaminophen (APAP) combination analgesics offer an established approach to multimodal pain management [1-3]. By utilizing agents with complimentary mechanisms of action; these combination formulations are intended to be additive; which may allow for the management of pain at a lower dose of each component; potentially reducing the risk of concentration-dependent adverse events [1,4-7]. Immediate-release (IR) oxycodone (OC)/APAP combinations are indicated for the management of moderate to severe pain [8-10] and have demonstrated clinical efficacy in a variety of painful conditions; including low back pain [2,4,11]; arthritis [4,12-15], cancer [4,16] and postoperative pain [4,17-20].

Oxycodone is a semisynthetic opioid analgesic with high bioavailability with 60% to 87% of oral dose from IR formulation reaching systemic circulation [21,22]. IR formulations of oxycodone produce a rapid rise in plasma levels (time to peak plasma concentrations [T_{max}]; ~1.0-2.6 hours) and have an elimination half-life ($t_{1/2}$) of 3.2 to 5 hours [22-24]. Because of the delivery profile; IR oxycodone is typically administered every 4 to 6 hours to maintain analgesia [22]. Extended-release (ER) oxycodone formulations are designed to maintain plasma concentrations of oxycodone for longer periods; thereby permitting less frequent dosing [22,25,26]. Fewer daily doses has been shown to provide some benefit over more frequently dosed agents by reducing the pill burden and improving treatment adherence [25,27-30].

Acetaminophen is a nonopioid; nonsalicylate analgesic/antipyretic that is believed to exert analgesic effects predominantly via central mechanisms [31]. When delivered in IR formulations; acetaminophen has high oral bioavailability (60% to 89%); with peak plasma levels occurring within 1 to 2 hours of administration [32]. It is extensively metabolized in the liver; with a $t_{1/2}$ of 1 to 4 hours [32,33].

MNK-795 (OC/APAP ER; Mallinckrodt Inc.; Hazelwood; MO; USA) is a bilayer product with both IR and ER components; designed to allow for 12-hour dosing. This oral combination analgesic was designed to release oxycodone and acetaminophen both immediately (IR component) and over time (ER component). The ER component releases the active ingredients at a steady rate in the upper gastrointestinal tract over an extended period of time. OC/APAP ER employs a dual-layer biphasic delivery mechanism that; when administered as a single dose (ie; 2 tablets); is designed so that the IR component delivers 3.75 mg oxycodone and 325 mg acetaminophen and the ER component delivers 11.25 mg oxycodone and 325 mg acetaminophen. The total

***Corresponding author:** Krishna Devarakonda, Mallinckrodt Inc., 675 James McDonnell Blvd 302-3-W, Hazelwood, MO 63042, USA, Tel: (314) 654-3364; Fax: (314) 654-9364; E-mail: krishna.devarakonda@mallinckrodt.com

Received January 09, 2014; **Accepted** February 24, 2014; **Published** March 04, 2014

Citation: Devarakonda K, Morton T, Giuliani M, Kostenbader K, Barrett T (2014) Single-Dose Pharmacokinetics of MNK-795, an Extended-Release Oxycodone and Acetaminophen Combination Analgesic: Results from 2 Active Comparator Studies. J Bioequiv Availab 6: 038-045. doi:10.4172/jbb.1000178

acetaminophen strength per tablet of OC/APAP ER is in accordance with the latest dose limitation imposed by the US Food and Drug Administration of 325 mg of acetaminophen per dosage unit; this also limits the total daily dose of acetaminophen to an amount that is below the current maximum total daily dose (4000 mg) [34].

The current studies were conducted in healthy participants to characterize the pharmacokinetics (PK) and bioavailability of OC/APAP ER. Study 1 was conducted to determine the PK; bioavailability; and dose proportionality of a single dose of 1 or 2 tablets of OC/APAP ER compared with an IR OC/APAP formulation. Study 2 was conducted to evaluate the single-dose PK and bioavailability of 2 tablets of OC/APAP ER compared with those following administration of marketed forms of IR oxycodone; IR tramadol/APAP; and IR OC/APAP. 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 from MNK795 (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 MNK795 and the IR comparator was still highly relevant for prescribing physicians; Percocet 7.5 mg OC/325 mg APAP was included in this study. Safety and tolerability were monitored throughout both studies.

Materials and Methods

Participants

In both studies; healthy men or nonlactating; nonpregnant women aged 18 to 55 years with a body mass index of 19 to 30 kg/m^2 and a minimum weight of 130 lb were eligible to participate in the study. Exclusion criteria included smoking or use of nicotine-containing products in the previous 6 months; history of drug or alcohol abuse 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 drug allergy; hypersensitivity; or intolerance of opioid products (including oxycodone) or acetaminophen (and tramadol in Study 2); history of any condition that could interfere with the absorption; distribution; metabolism; or excretion of the study medication; or previous gastric bypass or gastric band surgery.

Both studies were conducted according to Good Clinical Practice guidelines. Written informed consent was obtained from participants prior to enrollment; and the protocols were approved by the same institutional review board (IntegReview; Austin; TX; USA).

Study design and treatments

Both trials were single-center; open-label; randomized; phase 1; crossover studies. Study 1 was a 3-period study; in which completers of the first 3 periods entered a fourth treatment period that served as a second phase of the study. Participants were randomized to receive the following treatments in a 3-way crossover design under fasted conditions: 1) 1-tablet of OC/APAP ER (7.5 mg OC/325 mg APAP) taken once; 2) 2-tablets of OC/APAP ER (15 mg OC/650 mg APAP) taken once; and 3) 1-tablet of IR OC/APAP (Percocet®; Endo Pharmaceuticals; Malvern; PA; USA; 7.5 mg OC/325 mg APAP) taken twice; 6 hours apart (total; 15 mg OC/650 mg APAP). Participants who completed study 1 periods 1; 2; and 3 returned for period 4 and received 2 tablets of IR OC/APAP (7.5 mg OC/325 mg APAP) taken twice; 6 hours apart (total; 30 mg OC/1300 mg APAP) under fasted conditions.

In study 2; participants were randomly assigned to receive the following treatments in a 4-way crossover design under fasted conditions: 1) 2-tablets of OC/APAP ER (7.5 mg/325 mg) taken once (total; 15 mg OC/650 mg APAP); 2) 1-tablet of IR oxycodone (Roxicodone®; Mallinckrodt Inc.; Hazelwood; MO; USA; 15 mg) taken twice; 6 hours apart (total; 30 mg oxycodone); 3) 1-tablet of IR tramadol/APAP (Ultracet®; Janssen Pharmaceuticals; Inc.; Titusville; NJ; USA; 37.5 mg/325 mg) taken twice; 6 hours apart (total; 75 mg tramadol/650 mg APAP); and 4) 1-tablet IR OC/APAP (7.5 mg/325 mg) taken twice; 6 hours apart (total; 15 mg OC/650 mg APAP).

Both studies included a screening visit and 4 confinement periods of approximately 60 hours (study 1) and 48 hours (study 2); with a minimum of 7 days between the start of each period. Study 1 included follow-up period of 7 or 28 days for monitoring of ongoing treatment-emergent adverse events (AEs) or serious AEs (SAEs); respectively. In study 2; investigators followed up on all AEs and SAEs that were ongoing at study completion until the events subsided; abnormal measures returned to acceptable ranges; patients were referred to their usual physicians; or investigators deemed that additional follow-up was unnecessary. The total duration of study 1 was approximately 12 weeks; and study 2 lasted approximately 8 weeks.

Plasma sampling and assessments

Participants fasted for a minimum of 10 hours (overnight) before receiving a dose of study medication; a meal was provided approximately 4 hours after the first dose. In both studies; blood samples were collected predose (within 60 minutes of the first dose) and at 15; 30; 45 minutes; and 1; 2; 3; 4; 6; 6.5; 7; 8; 9; 10; 12; 16; 18; 20; 24; 36 hours after dosing by venipuncture. Study 1 investigators also collected samples at 5 and 48 hours after dosing. Whole blood samples were collected in tubes containing K_2 or K_3 EDTA as the anticoagulant. Plasma fractions were frozen within 1 hour of collection at ≤ −70°C.

Oxycodone and APAP concentrations were assessed; using a validated liquid chromatography–tandem mass spectrometry (LC-MS/MS) assay; at PPD Bioanalytical Lab; Middleton; Wisconsin; USA. The LC-MS/MS method was developed and validated over a calibration range of 0.100 to 100 ng/mL for oxycodone and 100 to 50;000 ng/mL for acetaminophen. Short and long term stability of OC and APAP in standards; controls and plasma samples were established over the required storage period. The quantitative LC-MS/MS method utilized OC-d_6 and APAP-d_4 as the internal standards. Human plasma containing oxycodone; acetaminophen; and OC-d_6 and APAP-d_4; was extracted; reconstituted and injected onto the instrument. Calibration curves (calculated using a linear-weighted; 1/concentration; least squares regression algorithm for oxycodone and a linear-weighted; 1/concentration^2; least squares regression algorithm for acetaminophen) were plotted as the peak area of the analyte to the internal standard versus concentration. Linearity was indicated by correlation coefficients >0.990 for each standard curve.

PK parameters (area under the plasma concentration-time curve from time 0 to the last quantifiable concentration [AUC_{0-t}]; area under the plasma concentration-time curve from time 0 to infinity [AUC_{0-inf}]; maximum plasma concentration [C_{max}]; T_{max}; lag time [t_{lag}; or time before the first measurable concentration]; apparent first-order terminal elimination rate constant [K_{el}]; and $t_{½}$) for oxycodone and APAP were calculated using Phoenix® WinNonlin® Version 6.1 (Pharsight Corporation; St. Louis; MO; USA).

In both studies; safety and tolerability were assessed using standard measures; including AE monitoring; clinical laboratory tests (urinalysis; serum chemistry; hematology; and serum pregnancy tests for females) performed at screening and at the conclusion of period 4 or at early termination; vital sign and pulse oximetry measurements; 12-lead electrocardiogram results; and physical examination findings. Participants also were evaluated for impaired judgment at early termination or at the completion of each period before being released from the clinic.

Statistics

Individual plasma concentrations versus actual time data were used to estimate PK parameters for oxycodone and APAP by standard noncompartmental methods. Linear mixed model analysis of variance (ANOVA) was performed to compare treatments using the dose-normalized (plasma concentration ÷ dose administered) natural log-transformed PK parameters ($AUC_{0\text{-}inf}$; $AUC_{0\text{-}t}$; and C_{max}) defined as the dependent variable; with sequence; treatment; and period as fixed effects and subjects nested within sequences as random effects; and nontransformed PK parameters (K_{el} and $t_{1/2}$) defined as the dependent variables; with sequence; treatment; and period as fixed effects; and subjects nested with sequences as random effects.

In study 1; the 1- and 2-tablet doses of IR OC/APAP were compared using a linear mixed model ANOVA on the natural log-transformed dose normalized PK parameter using treatment as a fixed effect and subject as a random effect. All other comparisons between treatments were performed as detailed earlier. Two tests for outliers (Grubbs' test and the Likelihood Distance Test) were used to evaluate $AUC_{0\text{-}inf}$; $AUC_{0\text{-}t}$; and C_{max} measures.

For both oxycodone and APAP; the geometric least squares (LS) means; ratio of geometric LS means; the corresponding 90% confidence interval (CI) for the ratio; and intrasubject variability were determined for dose-normalized parameters ($AUC_{0\text{-}inf}$; $AUC_{0\text{-}t}$; and C_{max}). LS means; difference of LS means; the 90%CI for the difference; and P values for testing fixed effects were calculated for the nontransformed parameters (K_{el} and $t_{1/2}$).

The Wilcoxon signed-rank test was performed to determine the statistical significance of the median difference for the non-transformed PK parameters T_{max} and t_{lag}. A P-value ≤ 0.05 was considered to be a significant difference between treatments.

A 90%CI of the geometric LS means ratios fully contained within 80% to 125% for $AUC_{0\text{-}inf}$; $AUC_{0\text{-}t}$; and C_{max} indicated no difference between treatments. Participant disposition; demographic; and baseline characteristics were characterized using descriptive statistics. Significance testing was 2-tailed using α=0.05; unless otherwise specified. All analyses were performed using SAS® software (SAS Institute; Inc.; Cary; North Carolina; USA).

Data from all dosed participants were included in the safety analyses for both studies. In study 1 the data from the primary completers group; which comprised all participants who completed the first 3 crossover periods; were used for the primary PK analysis of OC/APAP ER and secondary analysis of IR OC/APAP (one tablet). Data from the secondary completers group which comprised all participants who completed the fourth period (2 tablets of IR OC/APAP); were used for additional analyses. In study 2; data from the completers group (those who completed all 4 periods) were included in the PK analyses.

Results

Participants

Demographics and baseline characteristics of the participants were similar within each study and are shown in Table 1. In study 1; 48 participants were enrolled in the study; 33 (68.8%) of whom completed the first 3 treatment periods. Twenty-seven participants (56.3%) completed all 4 treatment periods. Twenty-one participants (43.8%) discontinued: 19 (39.6%) due to the AE of vomiting (per protocol) and 2 (4.2%) because withdrawal criteria were met (1 protocol violation of other use of acetaminophen; 1 positive urinary drug screen at check-in). In study 2; 48 participants were enrolled; and 30 (62.5%) completed all 4 treatment periods. Eighteen participants (37.5%) discontinued: 13 (27.1%) due to the AE of vomiting (per protocol); 3 (6.3%) met withdrawal criteria (positive urinary drug screen at check-in); and 2 (4.2%) of these subjects did not respond to attempts to follow-up on the resolution of AEs.

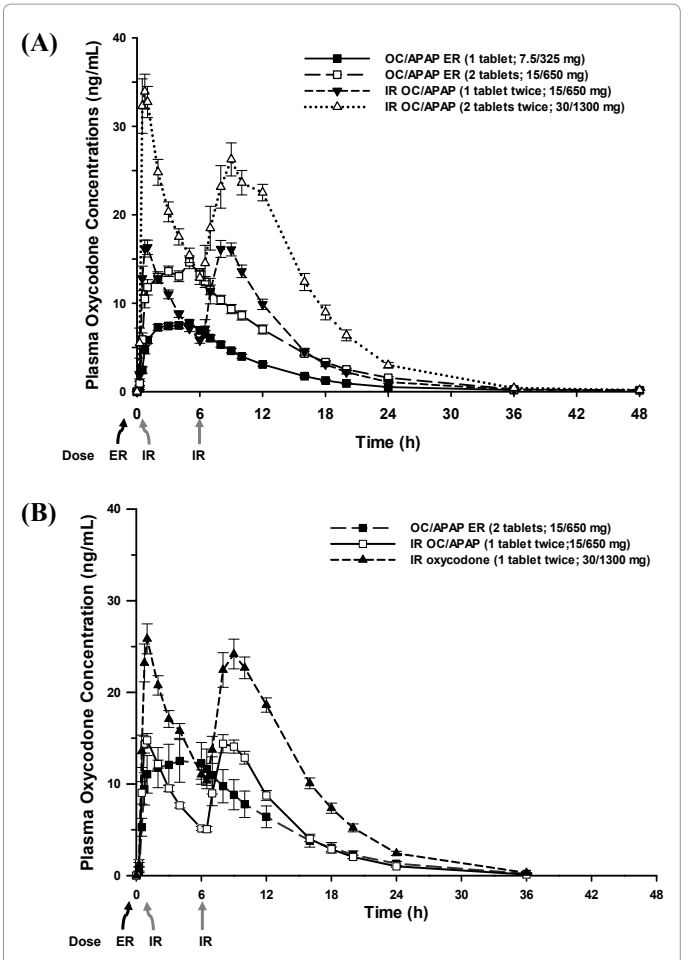
Oxycodone pharmacokinetics

Plasma concentrations of oxycodone over time for each of the treatments for both studies are shown in Figures 1A and 1B. In study 1; after the administration of OC/APAP ER (both 1- or 2-tablet doses); plasma concentrations of oxycodone rose rapidly without lag; similar to the concentrations observed with IR OC/APAP. Oxycodone was eliminated slowly; and mean oxycodone plasma concentrations were detectable through 36 hours after all treatments. The calculated estimates of oxycodone PK parameters for each of the 4 treatments are shown in Table 2.

Overall oxycodone exposure ($AUC_{0\text{-}t}$ and $AUC_{0\text{-}inf}$) increased proportionally with dose for both OC/APAP ER and IR OC/APAP and was comparable between the 2-tablet dose of OC/APAP ER and the 1-tablet dose of IR OC/APAP administered twice; 6 hours apart (total; 15 mg OC/650 mg APAP for both; $AUC_{0\text{-}t}$ of 186.0 and 191.2 ng•h/mL, respectively; $AUC_{0\text{-}inf}$ of 187.7 and 193.1 ng•h/mL, respectively). The geometric LS means ratios of dose-normalized oxycodone $AUC_{0\text{-}t}$ and $AUC_{0\text{-}inf}$ indicated that the bioavailability of oxycodone from 1 or 2 tablets of OC/APAP ER (administered once) and 1 tablet of IR OC/APAP (administered twice) were comparable; as values for all

	Study 1	Study 2
Characteristic	**All Dosed Participants (N=48)**	**All Dosed Participants (N=48)**
Age, y		
Mean (SD)	31.0 (9.31)	32.8 (9.89)
Range	20-53	18-53
Sex, n (%)		
Male	24 (50)	29 (60.4)
Female	24 (50)	19 (39.6)
Race, n (%)		
White	32 (66.7)	32 (66.7)
Black or African American	15 (31.3)	16 (33.3)
Asian	1 (2.1)	0 (0)
Ethnicity, n (%) Hispanic or Latino Not Hispanic or Latino	 14 (29.2) 34 (70.8)	 19 (39.6) 29 (60.4)
Weight, kg, mean (SD)	74.3 (9.9)	75.6 (9.2)
Body mass index, kg/m² Mean (SD) Range	 26.0 (2.6) 19.9-29.9	 26.6 (2.3) 21.6-29.9

Table 1: Summary of Participant Disposition.



[a]Data are from 29 participants who completed all 4 study periods

Figure 1: A. Mean (SE) plasma concentration of oxycodone versus time by treatment in study 1. **B.** Mean (SE) plasma concentration of oxycodone versus time by treatment in study 2[a] (B). Arrows indicate timing of doses.

comparisons were fully contained with the predefined no-difference range of 80% to 125%.

Similarly; the dose-normalized C_{max} for oxycodone with both doses of OC/APAP ER were comparable as the 90%CI s of the geometric LS means ratios for the 1-tablet dosing versus the 2-tablet dosing were fully contained within the predefined no-difference range (LS means ratio; 102.7%; 90%CI ; 97.3%-108.4%) indicating dose proportionality for oxycodone. However; the dose-normalized C_{max} for oxycodone with the 1-tablet and the 2-tablet doses of OC/APAP ER were approximately 18% and 21% lower; respectively; than the dose-normalized C_{max} for the 1-tablet dosing of IR OC/APAP (administered twice). The 90%CI s for the geometric LS means ratios for oxycodone C_{max} were only partially contained within the no-difference range (1-tablet OC/APAP ER vs IR OC/APAP; LS means ratio; 81.6%; 90%CI ; 77.3%-86.1%; 2-tablet OC/APAP ER vs IR OC/APAP; LS means ratio; 79.5%; 90%CI ; 75.3%-83.9%).

Intrasubject variability (CV) was about 9% for $AUC_{0-12hss}$ and 13% for C_{max} following administration of 1 or 2 OC/APAP ER tablets. Intersubject variability (CV) for AUC_{0-t}; AUC_{0-inf} and C_{max} for oxycodone after administration of 1 or 2 tablets of OC/APAP ER ranged from 25% to 28%.

In study 2; plasma concentrations of oxycodone also increased rapidly after OC/APAP ER (15/650 mg) administration without lag; similar to the rapid rise without lag observed with IR oxycodone (15 mg twice; 30 mg total) and IR OC/APAP (7.5/325 mg twice; 15/650 mg total). Oxycodone was eliminated slowly; mean plasma oxycodone levels from OC/APAP ER were approximately 45% of peak by 12 hours after dosing and were detectable through 24 hours. The calculated estimates of the PK parameters for oxycodone for each of the 3 treatments containing oxycodone are shown in Table 2.

In this study; the total dose-normalized systemic exposure to oxycodone from OC/APAP ER was comparable to oxycodone exposure from IR oxycodone and IR OC/APAP; as the 90%CIs of the ratios of geometric LS means of AUC_{0-t} and AUC_{0-inf} were fully contained within the predefined no-difference range of 80% to 125%. In addition; peak oxycodone concentrations from OC/APAP ER (dose-normalized) were equivalent to those achieved with IR oxycodone (LS means ratio; 92.2%; 90%CI; 85.1%-99.9%); but concentrations were 27% lower than those achieved with IR OC/APAP (LS means ratio; 72.5%; 90%CI; 66.9%-78.5%).

Intrasubject variability (CV) was about 10% for AUCs and 18% for C_{max} following administration of 2 OC/APAP ER tablets. Intersubject variability (CV) for AUC_{0-t}; AUC_{0-inf} and C_{max} for oxycodone after administration of 2 tablets of OC/APAP ER was about 21%.

Acetaminophen pharmacokinetics

Plasma concentrations for acetaminophen over time for both studies are shown in Figures 2A and 2B. In study 1; the plasma concentrations of acetaminophen rose rapidly without lag after administration of OC/APAP ER (both 1- or 2-tablet doses); similar to the rapid rise without lag observed with IR OC/APAP. Peak plasma acetaminophen concentrations occurred 45 minutes after OC/APAP ER dosing; acetaminophen concentrations at 7 to 12 hours after the 2-tablet dose of OC/APAP ER were lower than concentrations after the second dose of IR OC/APAP. The calculated estimates of the PK parameters for acetaminophen for each of the treatments are shown in Table 3. AUC and C_{max} for acetaminophen were comparable for 2 tablets of OC/APAP ER (15/650 mg) and the 1 tablet every 6 hours dose of IR OC/APAP (total; 15 mg OC/650 mg APAP). Dose-normalized AUC_{0-t}; AUC_{0-inf}; and C_{max} for acetaminophen were comparable across all treatment groups in study 1. A statistical comparison of the geometric LS means ratios of dose normalized acetaminophen AUC_{0-t}; AUC_{0-inf}; and C_{max} found that the 90%CIs of the geometric LS means ratios for 1- and 2-tablet doses of OC/APAP ER versus 1 tablet of IR OC/APAP were within 80 to 125%; indicating that the bioavailability of acetaminophen was similar between OC/APAP ER (1 or 2 tablets taken once) and IR OC/APAP (1 tablet twice). In addition; the 90%CIs for the comparison between 1- and 2-tablet doses of OC/APAP ER were also within this range for AUC_{0-t}; AUC_{0-inf}; and C_{max}; respectively; suggesting dose proportionality for the acetaminophen component of OC/APAP ER.

In study 2; the plasma concentrations of acetaminophen also increased rapidly without lag after OC/APAP ER administration. Peak plasma acetaminophen concentrations occurred 45 minutes after OC/APAP ER dosing and were 18% of peak by 12 hours after dosing. Acetaminophen plasma concentrations for OC/APAP ER fell below those for both comparators 8 hours after dosing (ie; 2 hours after the second dose of the comparator). The calculated estimates of the PK parameters for acetaminophen for each of the 3 treatments

	Study 1				Study 2		
Parameter[a]	**OC/APAP ER (1 Tablet; 7.5/325 mg) (n=33)**	**OC/APAP ER (2 Tablets; 15/650 mg) (n=33)**	**IR OC/APAP (1 Tablet Twice; 15/650 mg) (n=33)**	**IR OC/APAP (2 Tablets Twice; 30/1300 mg) (n=27)**	**OC/APAP ER (2 Tablets; 15/650 mg) (n=29)**	**IR Oxycodone (1 Tablet Twice; 30 mg OC) (n=29)**	**IR OC/APAP (1 Tablet Twice; 15/650 mg) (n=29)**
$AUC_{0\text{-}inf}$ (ng•h/mL)	89.9 (24.7)[b]	187.7 (47.6)	193.1 (53.2)	403.0 (110.5)	169.3 (37.0)	336.3 (62.8)	171.5 (34.1)
$AUC_{0\text{-}t}$ (ng•h/mL)	87.4 (24.6)	186.0 (47.6)	191.2 (53.4)	401.2 (110.6)	167.9 (36.8)	334.6 (62.5)	169.9 (34.2)
C_{max} (ng/mL)	8.41 (2.1)[c]	16.39 (4.3)[c]	20.82 (6.0)	41.24 (12.1)	14.3 (2.9)[c]	31.3 (8.2)[c]	19.4 (4.6)
T_{max} (h)	4.0 (0.8-5.9)[c]	3.0 (0.8-6.5)[c]	7.8 (0.5-10.0)	0.8 (0.5-12.0)	4.0 (0.8-12.0)[c]	8.0 (0.8-12.0)	8.0 (0.5-12.0)
t_{lag} (h)	0.00 (0.00-0.50)[c]	0.00 (0.00-0.52)	0.00 (0.00-0.25)	0.00 (0.00-0.25)	0.00 (0.00-0.25)	0.00 (0.00-0.27)	0.00 (0.00-0.25)
$t_{1/2}$ (h)	4.5 (0.78)[b,c]	4.9 (0.93)[c]	4.1 (0.89)	4.3 (1.02)	4.5 (0.58)[c,d]	3.9 (0.31)	4.0 (0.48)
K_{el} (h^{-1})	0.159 (0.031)[b,c]	0.147 (0.027)[c]	0.177 (0.035)	0.169 (0.042)	0.158 (0.022)[c,d]	0.180 (0.014)	0.176 (0.023)

[a]All data are mean (SD), except T_{max} and t_{lag}, which are median (minimum, maximum); [b]n=32; [c]Reached statistical significance vs immediate-release oxycodone/acetaminophen (1 tablet, twice); [d]Reached statistical significance vs immediate-release oxycodone

$AUC_{0\text{-}inf}$, area under the plasma concentration-time curve from time 0 to infinity; $AUC_{0\text{-}t}$, area under the plasma concentration-time curve from time 0 to the last quantifiable concentration; APAP, acetaminophen; C_{max}, maximum observed plasma concentration; ER, extended-release; IR, immediate release; K_{el}, apparent terminal elimination rate constant; OC, oxycodone; $t_{½}$, terminal elimination half-life; t_{lag}, lag time; T_{max}, time to maximum observed plasma concentration

Table 2: Pharmacokinetic Estimates for Oxycodone.

	Study 1				Study 2		
Parameter[a]	**OC/APAP ER (1 Tablet; 7.5/325 mg) (n=33)**	**OC/APAP ER (2 Tablets; 15/650 mg) (n=33)**	**IR OC/APAP (1 Tablet Twice; 15/650 mg) (n=33)**	**IR OC/APAP (2 Tablets Twice; 30/1300 mg) (n=27)**	**OC/APAP ER (2 Tablets; 15/650 mg) (n=29)**	**IR tramadol/APAP (1 Tablet Twice; 75/650 mg) (n=29)**	**IR OC/APAP (1 Tablet Twice; 15/650 mg) (n=29)**
$AUC_{0\text{-}inf}$ (ng·h/mL)	16995 (5073)	34836 (11067)[b]	34236 (10126)[b]	71949 (24234)[c]	30759 (7000)	30989 (6759)	30368 (7291)
$AUC_{0\text{-}t}$ (ng·h/mL)	15871 (4841)	32665 (10894)	33040 (9589)	69837 (22945)	29065 (6851)	29935 (6578)	29193 (6892)
C_{max} (ng/mL)	2632 (918)	5230 (2086)	4878 (1545)	10741 (4123)	4654 (1360)	4256 (1004)	4387 (1326)
T_{max} (h)	0.8 (0.3-2.0)	0.8 (0.3-4.0)	0.5 (0.3-9.0)	0.5 (0.3-12.0)	0.8 (0.5, 2.0)[e]	2.0 (0.5, 9.0)[d]	0.8 (0.3, 12.0)[e]
t_{lag} (h)	0.0 (0.0-0.5)[d]	0.0 (0.0-0.3)	0.0 (0.0-0.0)	0.0 (0.0-0.0)[d]	0.0 (0.0, 0.3)	0.0 (0.0, 0.5)	0.0 (0.00, 0.3)
$t_{1/2}$ (h)	5.3 (1.53)[d]	6.9 (2.15)[b,d]	4.4 (1.16)[b]	5.8 (1.47)[c,d]	5.8 (2.07)[d,e]	4.1 (1.08)	4.4 (1.24)
K_{el} (h^{-1})	0.142 (0.048)[d]	0.110 (0.034)[b,d]	0.167 (0.041)[b]	0.129 (0.037)[c,d]	0.133 (0.038)[d,e]	0.178 (0.040)	0.168 (0.044)

[a]All data are mean (SD), except T_{max} and t_{lag}, which are median (minimum, maximum); [b]n=32; [c]n=25; [d]Reached statistical significance vs immediate-release oxycodone/acetaminophen (1 tablet, twice); [e]Reached statistical significance vs immediate-release tramadol/acetaminophen

$AUC_{0\text{-}inf}$, area under the plasma concentration-time curve from time 0 to infinity; $AUC_{0\text{-}t}$, area under the plasma concentration-time curve from time 0 to the last quantifiable concentration; APAP, acetaminophen; C_{max}, maximum observed plasma concentration; ER, extended release; IR, immediate release; K_{el}, apparent terminal elimination rate constant; OC, oxycodone; $t_{½}$, terminal elimination half-life; t_{lag}, lag time; T_{max}, time to maximum observed plasma concentration

Table 3: Pharmacokinetic Estimates for Acetaminophen.

are shown in Table 3.The total dose-normalized systemic exposure to acetaminophen from OC/APAP ER in study 2 was comparable to acetaminophen exposure from IR tramadol/APAP and IR OC/APAP; with the 90%CI s of the ratios of geometric LS means for $AUC_{0\text{-}t}$; $AUC_{0\text{-}inf}$; and C_{max} all fully contained within the predefined no-difference range of 80% to 125%.

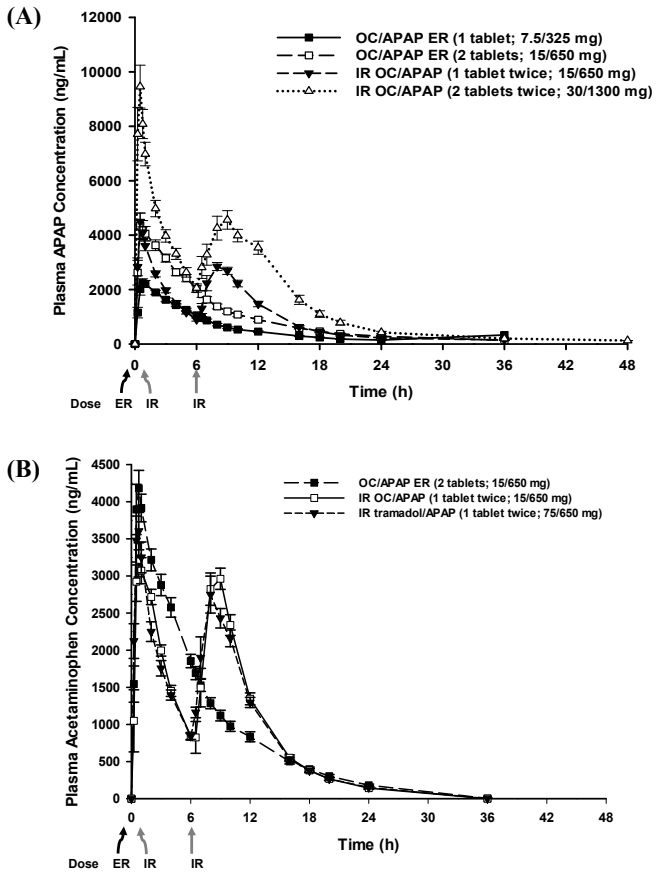
Across both studies; intrasubject variability (CV) was 5% to 6% for AUC and 15% to 19% for C_{max} for acetaminophen following administration of 1 or 2 OC/APAP ER tablets. Intersubject variability (CV) for $AUC_{0\text{-}t}$; $AUC_{0\text{-}inf}$ and C_{max} for acetaminophen after administration of 1 or 2 tablets of OC/APAP ER ranged from 24% to 33% for AUC and 29% to 40% for C_{max}.

Safety/Tolerability

AEs for both studies are reported in Table 4. In study 1; 41 of 48 total participants (85.4%) experienced at least 1 AE; with 40 participants (83.3%) experiencing AEs that were considered by the investigators to be treatment-related. AEs rates were higher while participants were receiving 2 tablets of IR OC/APAP every 6 hours (75.8%) than the rate of AEs seen with OC/APAP ER (25.6% and 51.2% for 1 and 2 tablets; respectively) and 1 tablet of IR OC/APAP (56.4%). There were no severe AEs or SAEs at any point in the study.

Overall; across all treatment conditions; the most frequently reported AEs were nausea (68.8%); vomiting (39.6%); somnolence (35.4%); pruritus (33.3%); and headache (29.2%). The incidence of these AEs during 2-tablet dosing of OC/APAP ER was 29.3%; 17.1%; 12.2%; 7.3%; and 19.5%; respectively. Nineteen participants who experienced moderate vomiting were discontinued from the study based on the protocol requirement.

In study 2; 29 of 48 enrolled participants (60.4%) experienced AEs. More participants reported AEs after receiving 1 tablet of IR oxycodone twice (58.1%) than after receiving 1 tablet of IR OC/APAP twice (37.5%); 2 tablets OC/APAP ER given once (23.1%); or IR tramadol/APAP given twice (22.2%). No SAEs were reported during the study. The most common AEs overall were nausea (43.8%); dizziness (33.3%); vomiting (27.1%); headache (20.8%); somnolence (10.4%); feeling hot (10.4%); and pruritus (10.4%). The incidence of common AEs after receiving 2 tablets of OC/APAP ER was 12.8% for nausea; 7.7% each for dizziness and somnolence; and 2.6% each for vomiting; pruritus; headache; abdominal pain; feeling abnormal; euphoric mood



[a]Data are from 29 participants who completed all 4 study periods

Figure 2: A. Mean (SE) plasma concentration of acetaminophen versus time by treatment in study 1. **B.** Mean (SE) plasma concentration of acetaminophen versus time by treatment in study 1 (A) and study 2[a] (B). Arrows indicate timing of doses.

and feeling hot. Thirteen participants (27.1%) were withdrawn from the study due to vomiting (per protocol): 10 (23.3%) after receiving IR oxycodone; and 1 each after receiving 2 tablets of OC/APAP ER (2.6%); 1 tablet of IR tramadol/APAP (2.8%); or 1 tablet of IR OC/APAP (2.5%).

No apparent clinically significant treatment-related trends in clinical laboratory assessments or physical examination findings were observed in either study; with the exception of 1 participant who experienced elevated bilirubin (mild; possibly related to study drug) in study 1. At screening; this participant had a normal level of serum bilirubin (1.2 mg/dL; normal range 0.2 to 1.3 mg/dL); which increased to 1.9 mg/dL on the first day of treatment (IR OC/APAP); she was followed for 7 days in the study and then referred to her primary physician.

Discussion

OC/APAP ER is indicated for the treatment of acute pain. The formulation is designed to reach therapeutic levels of both opioid and non-opioid drugs quickly (within 1 hour) through the IR layer component; with sustained analgesia over the dosing interval (12 hours) due to the ER layer component. Therefore; a lag (tlag) similar to IR comparators is desirable. In this single-dose PK studies; administration of 1 or 2 tablets of OC/APAP ER resulted in a rapid rise of both oxycodone and acetaminophen plasma levels without lag. Plasma oxycodone concentrations peaked at 3 to 4 hours postdose and were sustained beyond the 12-hour dosing period; and plasma acetaminophen concentrations peaked at about 45 minutes postdose and tapered off by 7 to 12 hours following administration. Peak plasma levels of oxycodone were approximately 18% to 27% lower for OC/APAP ER than for IR OC/APAP; which may theoretically translate into reduced risk for oxycodone concentration-dependent adverse events. In these 2 cross-over studies; following administration of 1 or 2 tablets of OC/APAP ER the intrasubject variability (within subject) remained low and the intersubject variability (across subjects) was similar for AUC for both oxycodone and acetaminophen. The intersubject variability for oxycodone C_{max} was lower for OC than for APAP. Both studies demonstrated that the overall exposure (AUC_{0-t}; AUC_{0-inf}) to both oxycodone and acetaminophen were comparable for OC/APAP ER administered once and IR formulations (IR oxycodone; IR tramadol/APAP; and IR OC/APAP) administered twice; 6 hours apart. Therefore; in these 2 phase 1; PK studies in healthy adults; the total systemic exposure and extent of absorption of oxycodone and acetaminophen were comparable between OC/APAP ER (1 or 2 tablets once) and IR OC/APAP (1 tablet twice) under fasted conditions.

OC/APAP ER was generally well tolerated in these 2 PK studies in healthy adults. AEs occurring after OC/APAP ER administration were consistent with those observed with other opioids [35,36]; and similar to those occurring after administration of IR OC/APAP and IR tramadol/APAP in the current studies. The most commonly reported AEs were gastrointestinal and central nervous system events. Gastrointestinal side effects are common among opioid users and are often cited as a reason for premature treatment discontinuation [35,36]. In the current studies; rates of gastrointestinal AEs and discontinuations due to vomiting were dose-dependent and; as would be expected; were highest during administration of IR oxycodone and 2-tablet doses of IR OC/APAP; which delivered a total of 30 mg oxycodone. The incidence of adverse events; including nausea and vomiting; was higher in study 1 than in study 2 for the 15/650 mg doses of OC/APAP ER and IR OC/APAP 15/650 mg.

The results of these studies demonstrate that OC/APAP ER administered once exhibits absorption and bioavailability of oxycodone and acetaminophen similar to what has been observed with various IR products administered twice; 6 hours apart. These findings demonstrate that dosing OC/APAP ER will provide comparable PK to IR OC/APAP with less frequent dosing. In addition; the low plasma concentrations of acetaminophen 12 hours after a single administration of OC/APAP ER suggest little accumulation of acetaminophen may occur after repeated dosing with OC/APAP ER. This is important because overdose or accumulation of acetaminophen can overwhelm the acetaminophen detoxification process and lead to liver injury [37,38]. Following acute acetaminophen ingestion; individuals with plasma levels above 200 mcg/mL at 4 hours post ingestion and 25 mcg/mL at 16 hours post ingestion are at risk of developing acetaminophen –associated liver injury; with repeated supratherapeutic ingestion; levels greater than 10 mcg/mL are associated with increased risk of liver injury [39]. The acetaminophen dose and delivery with OC/APAP ER may provide a margin of safety if additional acetaminophen is consumed inadvertently.

	Study 1				Study 2			
AE, n (%)	**OC/APAP ER (1 Tablet; 7.5/325 mg) (n=39)**	**OC/APAP ER (2 Tablets; 15/650 mg) (n=41)**	**IR OC/APAP (1 Tablet Twice; 15/650 mg) (n=39)**	**IR OC/APAP (2 Tablets Twice; 30/1300 mg) (n=33)**	**OC/APAP ER (2 Tablets; 15/650 mg) (n=39)**	**IR Oxycodone (1 Tablet Twice; 30 mg OC) (n=43)**	**IR tramadol/APAP (1 Tablet Twice; 75/650 mg) (n=36)**	**IR OC/APAP (1 Tablet Twice; 15/650 mg) (n=40)**
Any AE	10 (25.6)	21 (51.2)	22 (56.4)	25 (75.8)	9 (23.1)	25 (58.1)	8 (22.2)	15 (37.5)
Nausea	4 (10.3)	12 (29.3)	12 (30.8)	17 (51.5)	5 (12.8)	15 (34.9)	3 (8.3)	9 (22.5)
Vomiting	2 (5.1)	7 (17.1)	4 (10.3)	6 (18.2)	1 (2.6)	10 (23.3)	1 (2.8)	1 (2.5)
Somnolence	2 (5.1)	5 (12.2)	5 (12.8)	9 (27.3)	3 (7.7)	2 (4.7)	0 (0.0)	3 (7.5)
Pruritus	0	3 (7.3)	5 (12.8)	12 (36.4)	1 (2.6)	5 (11.6)	0 (0.0)	1 (2.5)
Headache	2 (5.1)	8 (19.5)	5 (12.8)	4 (12.1)	1 (2.6)	5 (11.6)	3 (8.3)	3 (7.5)
Dizziness	1 (2.6)	4 (9.8)	4 (10.3)	7 (21.2)	3 (7.7)	10 (23.3)	2 (5.6)	4 (10.0)
Feeling Hot	0	2 (4.9)	3 (7.7)	3 (9.1)	1 (2.6)	2 (4.7)	0 (0.0)	2 (5.0)

AE, adverse event
*AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA®; MedDRA MSSO, McLean, VA, USA)

Table 4: Summary of Most Frequently Occurring Adverse Events*.

While the results of these studies are promising; there are limitations; primarily the use of a small sample size of healthy participants in a fasted state. However; this is common for PK studies; and the AEs reported with these studies were similar to what is expected with this type of medication [35,36]. Another potential limitation of these studies is that the time to reach peak oxycodone plasma concentrations cannot be easily compared between the single- and multiple-administration conditions. The T_{max} after administration of OC/APAP ER (7.5/325 mg and 15/650 mg) was approximately 3 to 4 hours; whereas this value was reached at 7 to 8 hours (approximately 1.5 to 2 hours after the second dose) following administration of IR oxycodone and IR OC/APAP (15/650 mg). A higher peak after the second dose would generally be expected due to the presence of oxycodone when the second dose was administered. This was not demonstrated with all IR conditions; however; the T_{max} for oxycodone from IR OC/APAP (30/1300 mg) in study 1 occurred 45 minutes after the first dose; which may reflect "blunting" of the second peak. The presence of oxycodone after the first dose of IR OC/APAP may slow the motility of the gastrointestinal tract; slowing the absorption from subsequent doses and resulting in lower peaks [40]. The T_{max} for IR oxycodone has been previously reported to be approximately 1.4 to 2.6 hours with 15 and 30 mg dosing [23,24]; which is consistent with a T_{max} of 1.5 to 2 hours seen after the second dose in the current studies.

Conclusions

In these single-dose PK studies; the bioavailability of oxycodone and APAP were generally comparable between OC/APAP ER (1 or 2 tablets once) and IR OC/APAP (1 tablet twice) administered under fasted conditions. OC/APAP ER demonstrated a biphasic delivery of oxycodone; with a rapid rise in oxycodone concentrations similar to that observed with IR OC/APAP; and a slow decrease in plasma concentrations over 12 hours. Plasma concentrations of APAP also demonstrated rapid absorption; but tapered off 7 to 12 hours postdose.

Dose proportionality was observed between the 1-tablet and 2-tablet doses of OC/APAP ER. In addition; in these PK studies performed in healthy adults; OC/APAP ER was generally well tolerated; with the most frequently reported AEs being nausea; headache; vomiting; and somnolence. These findings demonstrate that OC/APAP ER yields plasma concentrations comparable to those of IR OC/APAP with less frequent dosing (every 12 hours); with a tolerability profile consistent to those seen with opioid analgesics.

Acknowledgment

Technical editorial and medical writing support for the development of this manuscript was provided by Lisa Bergstrom; PhD; James Bergstrom; PhD; and Mary Tom; Pharm D; Synchrony Medical Communications; LLC; West Chester; PA. Funding for the technical editorial and medical writing support was provided by Mallinckrodt Inc.; Hazelwood; MO.

References

1. Cooper SA, Precheur H, Rauch D, Rosenheck A, Ladov M, et al. (1980) Evaluation of oxycodone and acetaminophen in treatment of postoperative dental pain. Oral Surg Oral Med Oral Pathol 50: 496–501.
2. Gammaitoni AR, Galer BS, Lacouture P, Domingos J, Schlagheck T (2003) Effectiveness and safety of new oxycodone/acetaminophen formulations with reduced acetaminophen for the treatment of low back pain. Pain Med 4: 21–30.
3. Vickers A, Bali S, Baxter A, Bruce G, England J, et al. (2009) Consensus statement on the anticipation and prevention of acute postoperative pain: multidisciplinary RADAR approach. Curr Med Res Opin 25: 2557–2569.
4. Gatti A, Sabato E, Di Paolo AR, Mammucari M, Sabato AF (2010) Oxycodone/paracetamol: a low-dose synergic combination useful in different types of pain. Clin Drug Investig 30: 3–14.
5. Raffa RB, Pergolizzi JV, Segarnick DJ, Tallarida RJ (2010) Oxycodone combinations for pain relief. Drugs Today (Barc) 46: 379–398.
6. Raffa RB (2001) Pharmacology of oral combination analgesics: rational therapy for pain. J Clin Pharm Ther 26: 257–264.
7. Raffa RB, Pergolizzi JV, Jr. (2012) Multi-mechanistic analgesia for opioid-induced hyperalgesia. J Clin Pharm Ther 37: 125–127.
8. Percocet® (oxycodone and acetaminophen tablets, USP) [package insert]. Malvern, PA: Endo Pharmaceuticals, Inc, 2013.
9. Oxycodone and acetaminophen (oxycodone hydrochloride and acetaminophen) tablet [package insert]. Atlanta, GA: Mikart, Inc., 2007.
10. Endocet® (oxycodone hydrochloride and acetaminophen) tablets [package insert]. Chadds Ford, PA: Endo Pharmaceuticals, Inc., 2011.
11. Palangio M, Morris E, Doyle RT, Jr., Dornseif BE, Valente TJ (2002) Combination hydrocodone and ibuprofen versus combination oxycodone and acetaminophen in the treatment of moderate or severe acute low back pain. Clin Ther 24: 87–99.
12. Caldwell JR, Hale ME, Boyd RE, Hague JM, Iwan T, et al. (1999) Treatment of osteoarthritis pain with controlled release oxycodone or fixed combination oxycodone plus acetaminophen added to nonsteroidal antiinflammatory drugs: a double blind, randomized, multicenter, placebo controlled trial. J Rheumatol 26: 862–869.
13. Corsinovi L, Martinelli E, Fonte G, Astengo M, Sona A, et al. (2009) Efficacy of oxycodone/acetaminophen and codeine/acetaminophen vs. conventional therapy in elderly women with persistent, moderate to severe osteoarthritis-related pain. Arch Gerontol Geriatr 49: 378–382.
14. Gatti A, Sabato AF, Carucci A, Bertini L, Mammucari M, et al. (2009) Adequacy

assessment of oxycodone/paracetamol (acetaminophen) in multimodal chronic pain: a prospective observational study. Clin Drug Investig 29: 31–40.

15. Raffaeli W, Pari C, Corvetta A, Sarti D, Di S, V, et al. (2010) Oxycodone/acetaminophen at low dosage: an alternative pain treatment for patients with rheumatoid arthritis. J Opioid Manag 6: 40–46.

16. Sima L, Fang WX, Wu XM, Li F (2012) Efficacy of oxycodone/paracetamol for patients with bone-cancer pain: a multicenter, randomized, double-blinded, placebo-controlled trial. J Clin Pharm Ther 37: 27–31.

17. Gammaitoni AR, Galer BS, Bulloch S, Lacouture P, Caruso F, et al. (2003) Randomized, double-blind, placebo-controlled comparison of the analgesic efficacy of oxycodone 10 mg/acetaminophen 325 mg versus controlled-release oxycodone 20 mg in postsurgical pain. J Clin Pharmacol 43: 296–304.

18. Gaskell H, Derry S, Moore RA, McQuay HJ (2009) Single dose oral oxycodone and oxycodone plus paracetamol (acetaminophen) for acute postoperative pain in adults. Cochrane Database Syst Rev: CD002763.

19. Korn S, Vassil TC, Kotey PN, Fricke JR, Jr. (2004) Comparison of rofecoxib and oxycodone plus acetaminophen in the treatment of acute pain: a randomized, double-blind, placebo-controlled study in patients with moderate to severe postoperative pain in the third molar extraction model. Clin Ther 26: 769–778.

20. Palangio M, Wideman GL, Keffer M, Landau CJ, Morris E, et al. (2000) Combination hydrocodone and ibuprofen versus combination oxycodone and acetaminophen in the treatment of postoperative obstetric or gynecologic pain. Clin Ther 22: 600–612.

21. Ordoñez Gallego A, González Barón M, Espinosa Arranz E (2007) Oxycodone: a pharmacological and clinical review. Clin Transl Oncol 9: 298–307.

22. Lugo RA, Kern SE (2004) The pharmacokinetics of oxycodone. J Pain Palliat Care Pharmacother 18: 17–30.

23. Roxicodone® (oxycodone hydrochloride tablets USP) [package insert]. Newport, KY: Xanodyne Pharmaceuticals, Inc, 2012.

24. Reder RF, Oshlack B, Miotto JB, Benziger DD, Kaiko RF (1996) Steady-state bioavailability of controlled-release oxycodone in normal subjects. Clin Ther 18: 95–105.

25. McCarberg BH, Barkin RL (2001) Long-acting opioids for chronic pain: pharmacotherapeutic opportunities to enhance compliance, quality of life, and analgesia. Am J Ther 8: 181–186.

26. Amabile CM, Bowman BJ (2006) Overview of oral modified-release opioid products for the management of chronic pain. Ann Pharmacother 40: 1327–1335.

27. Graziottin A, Gardner-Nix J, Stumpf M, Berliner MN (2011) Opioids: how to improve compliance and adherence. Pain Pract 11: 574–581.

28. Claxton AJ, Cramer J, Pierce C (2001) A systematic review of the associations between dose regimens and medication compliance. Clin Ther 23: 1296–1310.

29. van Dulmen S, Sluijs E, van Dijk L, de Ridder D, Heerdink R, et al. (2007) Patient adherence to medical treatment: a review of reviews. BMC Health Serv Res 7: 55.

30. Richter A, Anton SE, Koch P, Dennett SL (2003) The impact of reducing dose frequency on health outcomes. Clin Ther 25: 2307–2335.

31. Smith HS (2009) Potential analgesic mechanisms of acetaminophen. Pain Physician 12: 269–280.

32. Meredith TJ, Goulding R (1980) Paracetamol. Postgrad Med J 56: 459–473.

33. Bertolini A, Ferrari A, Ottani A, Guerzoni S, Tacchi R, et al. (2006) Paracetamol: new vistas of an old drug. CNS Drug Rev 12: 250–275.

34. Kux L (2011) Prescription drug products containing acetaminophen, actions to reduce liver injury from unintentional overdose. Federal Register 76: 2691–2697.

35. Sinatra R (2010) Causes and consequences of inadequate management of acute pain. Pain Med 11: 1859–1871.

36. Moskovitz BL, Benson CJ, Patel AA, Chow W, Mody SH, et al. (2011) Analgesic treatment for moderate-to-severe acute pain in the United States: patients' perspectives in the Physicians Partnering Against Pain (P^3) survey. J Opioid Manag 7: 277–286.

37. Stirnimann G, Kessebohm K, Lauterburg B (2010) Liver injury caused by drugs: an update. Swiss Med Wkly 140: w13080.

38. Larson AM (2007) Acetaminophen hepatotoxicity. Clin Liver Dis 11: 525–548, vi.

39. Hodgman MJ, Garrard AR (2012) A review of acetaminophen poisoning. Crit Care Clin 28: 499–516.

40. Reisine T and Pasternak G (1996) Opioid analgesics and antagnosists. In: Goodman Gilman, A., eds. The Pharmacological Basis of Therapeutics. McGraw-Hill, New York, NY, pp 521–532.