Pain Medicine

Pain Medicine 2015; 16: 2142–2151
Wiley Periodicals, Inc.

Comparing the Effect of Tampering on the Oral Pharmacokinetic Profiles of Two Extended-Release Oxycodone Formulations with Abuse-Deterrent Properties

Jeff Gudin, MD,* Naama Levy-Cooperman, PhD,† Ernest A. Kopecky, PhD,‡ and Alison B. Fleming, PhD‡

*Pain Management Center, Englewood Hospital and Medical Center, Englewood, New Jersey, USA; †Altreos Research Partners Inc, Toronto, Ontario, Canada; ‡Collegium Pharmaceutical, Canton, Massachusetts, USA

Reprint requests to: Alison Fleming, PhD, Collegium Pharmaceutical, Inc., 780 Dedham St., Canton, MA, 02021, USA. Tel.: 781-713-3699; Fax.: 401-762-2043; E-mail: afleming@collegiumpharma.com.

Disclosure\Conflict of interest: Drs. Kopecky and Fleming are full-time employees of Collegium Pharmaceutical, Inc. Dr. Gudin has received speakers bureau or consulting fees from Collegium, Alere, Purdue, Salix, AstraZeneca, Xenoport, Iroko, Teva, Egalet, Zogenix, Insys, and Depomed

Funding sources: This study was funded by Collegium Pharmaceutical, Inc.

Abstract

Objective. Oxycodone DETERx® is an extended-release (ER), microsphere-in-capsule abuse-deterrent-formulation designed to retain its extended-release properties following tampering or misuse (e.g., chewing, crushing). This study assessed the safety and pharmacokinetics of orally administered intact and crushed Oxycodone DETERx® capsules compared with intact and crushed reformulated OxyContin® tablets and crushed immediate-release oxycodone tablets (IR oxycodone).

Methods. This was a randomized, open-label, active-controlled, cross-over study. Healthy subjects received five oxycodone treatments (40 mg) with a standardized high-fat, high-calorie meal: Oxycodone DETERx® (intact or crushed), OxyContin® (intact or crushed), and IR oxycodone (crushed). Blood samples were collected for assessment of oxycodone plasma concentrations.

Results. Thirty-eight subjects completed the study. Both crushed and intact Oxycodone DETERx® resulted in lower peak plasma concentrations when compared with IR oxycodone. Crushed Oxycodone DETERx® was bioequivalent to intact Oxycodone DETERx® and exhibited a numerically lower C_{max}. Also, median T_{max} was unchanged by crushing. In contrast, mean peak plasma oxycodone concentrations for crushed OxyContin® were significantly higher compared with intact OxyContin® and were bioequivalent to IR oxycodone. Median T_{max} for crushed OxyContin® was the same as IR oxycodone and 3.25 hours shorter than intact OxyContin®.

Conclusions. These data demonstrate that when crushed and taken orally, Oxycodone DETERx® maintains its EXTENDED-release profile, while crushed OxyContin® shows a pharmacokinetic profile similar to an immediate-release product. These results suggest that Oxycodone DETERx® may be less attractive to illicit drug users compared with existing abuse-deterrent-formulations, while providing a safer option for patients who may unknowingly crush their medication such as those who have difficulty swallowing.

Key Words. Abuse; Opioids; Oxycodone DETERx®; Pharmacokinetics; OxyContin®; Abuse-Deterrent; Tamper; Extended-Release

Introduction

The use of opioids to treat chronic pain has increased substantially over the past few years [1,2]; when used as prescribed, opioid analgesics can improve quality of life for patients suffering from chronic pain. However, as the medical use of opioids increased, so have the reported rates of misuse, abuse, and subsequent drug-related deaths [3–5]. In 2013, approximately 4.5 million individuals aged 12 and older reported past month non-medical use of prescription opioids [6], while emergency department visits associated with abuse or misuse of opioids in the United States increased from an estimated 172,738 in 2004 to an estimated 488,004 in 2011. This amounts to an ~183% increase in less than 10 years [7]. More recent data suggest that abuse of prescription opioids may be stabilizing or decreasing due to a number of possible factors including decreases in the number of prescriptions filled, the introduction of abuse-deterrent opioid formulations (ADFs) and local, state, and federal programs to improve opioid-prescribing practices [8,9]. Although abuse-related concerns associated with chronic opioid therapy are critical, care must be taken not to deprive those patients in pain who have a legitimate medical need for opioid analgesics.

Extended-release (ER) opioid formulations offer several clinical advantages including the convenience of less frequent dosing, decreased fluctuations in plasma levels, more consistent analgesia over the dosing period, and less night-time awakening due to pain [10,11]. Although ER formulations offer numerous clinical benefits, they are at particular risk for abuse via unintended routes because they contain higher amounts of the active drug compared with immediate-release (IR) formulations. When most ER formulations are altered or tampered with (e.g., by crushing or chewing), much, if not all of the active drug can be released more rapidly. This rapid onset increases the positive subjective and euphoric effects or "high" of an abusable drug, and consequently increases the attractiveness of such a drug for abuse [12].

A number of risk management approaches have been recommended to mitigate prescription opioid abuse and misuse, one of which is the development of ADFs designed to discourage abuse via specific routes of administration, while preserving analgesic benefits for patients [13,14]. In 2013, the US Food and Drug Administration (FDA) released a draft guidance document on the evaluation of abuse-deterrent opioids, which outlines the studies that should be conducted during development and following approval of these agents. This guidance was finalized in April of 2015. The studies outlined in the guidance are broken down into four categories and include laboratory-based in vitro manipulation (mechanical) and extraction (chemical) studies, pharmacokinetic studies to build on the manipulation or extraction data collected from *in vitro* studies, clinical abuse potential studies, also known as human abuse potential (HAP) or human abuse liability (HAL) studies, and postmarketing studies to identify whether the potential ADF results in a significant and persistent decrease in abuse once marketed.

A number of approaches can be taken in the development of ADFs; the guidance briefly outlines the different classifications, commonly categorized as physical-barrier, agonist-antagonist, aversion, or prodrug [15,16]. Physical-barrier or physicochemical formulations include properties that render the product difficult to crush or chew. These formulations, which often include excipients that result in larger and harder tablets, are effective in deterring illicit use, while also protecting patients with chronic pain who may mistakenly crush, break, and/or grind their opioid analgesics to facilitate swallowing the tablet or capsule [17]. However, there are a number of patients with chronic pain using opioids who have difficulty swallowing tablets and capsules and must resort to manipulation of the dosage form to successfully ingest their medication. The currently available physicochemical ADFs (e.g., reformulated OxyContin® [Purdue Pharma, LP, Stamford, CT]) do not address the need for a dosage form that can be administered via alternate routes such as cutting the tablet into small pieces or sprinkling onto food, while still retaining abuse deterrent properties, and these ADFs usually lose a substantial proportion of their ER properties when ground or crushed [18].

Oxycodone DETERx® (Collegium Pharmaceutical, Inc., Canton, MA) is an ER, microsphere-in-capsule formulation, designed to retain its ER properties following common tampering methods. The small particle size of Oxycodone DETERx® microspheres also allows for clinical advantages such as administration via enteral tube or by sprinkling onto soft food, thereby enabling a continuum of care for patients who initially can consume oral capsules, but subsequently develop swallowing difficulty, which may occur with a variety of clinical conditions or disease states.

Two recent studies were completed with Oxycodone DETERx®. The first examined the most effective tampering approaches for Oxycodone DETERx® (*in vitro* manipulation study) and the second, an *in vivo* study, evaluated the impact of the most aggressive mechanical manipulation methods and chewing on the pharmacokinetics of Oxycodone DETERx®. Results of these studies revealed that despite aggressive manipulation, Oxycodone DETERx® microspheres retained their ER properties in both a fed and fasted state [19].

The purpose of this study was to compare the pharmacokinetics and safety (under naltrexone blockade) of intact and crushed Oxycodone DETERx® with intact and crushed reformulated OxyContin® when both products are administered with food and to compare both with crushed IR oxycodone, also administered with food. In this study, the pharmacokinetic profile of Oxycodone DETERx® when manipulated was examined

when ingested in the presence of food, as this is a common form of administration in the intended patient population.

Methods

This was a randomized, open-label, single-dose, five-treatment, active-controlled, naltrexone-blocked, cross-over comparison study. The study was conducted at a single-center in the United States (Hackensack, NJ) in accordance with the International Conference on Harmonization and Good Clinical Practice guidelines, FDA regulations governing clinical study conduct, and the Declaration of Helsinki (and its amendments). Study materials were reviewed by an independent ethics review committee (IntegReview Ethics Review Board, Austin, TX) as required by local regulations. All subjects provided written informed consent after a complete explanation of the study and before any study-related procedures were performed. Subjects were informed that they could discontinue the study at any time.

Subjects

During a standard medical screening visit, potential subjects were evaluated for study eligibility. Subjects were healthy males and females (aged 18–50 years inclusive), with no clinically significant abnormalities on medical history, vital signs, physical examination, 12-lead electrocardiogram, or clinical laboratory tests. Subjects with a history of drug or alcohol abuse were excluded, as were regular users of tobacco products, subjects with intolerance or difficulty with venipuncture, subjects with known allergies to any of the test products, and subjects with a disorder or condition that may have interfered with drug absorption. Subjects were required to have a negative urine drug screen, saliva alcohol test, and urine cotinine test at the Screening visit and at admission to each Treatment Period. To minimize the risk of interaction, subjects were restricted from using other prescription or nonprescription drugs (except acceptable forms of birth control and acetaminophen), herbal remedies, or nutritional supplements during the study. Subjects were also told to avoid caffeine and alcohol for 24 hours prior to admission to each Treatment Period and were to abstain from food containing grapefruit, pomegranate, pomelo, and poppy seeds from 1 week prior to Treatment Period 1 until the end of the study. Female subjects of childbearing potential were required to be nonpregnant and nonlactating, had to use acceptable methods of contraception during the study, and were required to have a negative urine pregnancy test before dosing in each treatment period.

Overall Study Design

This five-way cross-over study included a 21-day Screening Phase, followed by a five-period Treatment Phase in which subjects received single oral doses of intact Oxycodone DETERx® 40 mg (expressed as HCl equivalents), crushed Oxycodone DETERx® 40 mg, intact OxyContin® 40 mg, crushed OxyContin® 40 mg, and crushed IR oxycodone 40 mg in a randomized order. At each of the five Treatment Periods, subjects were admitted to the research unit the day before dosing at which time they received an oral dose of 50 mg naltrexone (approximately 13 hours prior to dosing) to ensure that they were able to tolerate naltrexone dose. If subjects were able to tolerate the naltrexone, they were given a second 50 mg dose of naltrexone 1 hour prior to study drug dosing as a safety precaution. Subjects were assigned to 1 of 10 treatment sequences according to a two 5 × 5 "Williams Square" randomization design and received one dose of each of the assigned treatments following an overnight fast of at least 10 hours. Subjects started a standardized high-fat, high-calorie (HFHC) breakfast (approximately 150, 250, and 500–600 calories from protein, carbohydrate, and fat, respectively, as per Guidance for Industry: Food Effect Bioavailability and Fed Bioequivalence Studies, 2002) 30 minutes prior to the scheduled dosing time. Subjects were required to consume the meal within 20 minutes. Subjects who were not able to finish their standardized HFHC meal within the allotted time were not dosed and were discontinued from the study. All subjects were required to fast for at least 4 hours following dosing. Subjects were allowed to consume water freely other than 1 hour before and after drug administration.

For Oxycodone DETERx® and OxyContin® Treatment Periods, serial blood samples for pharmacokinetic evaluation were collected predose and for 36 hours postdose. For IR oxycodone, pharmacokinetic were collected predose and for 24 hours postdose. Subjects were to be deemed medically stable by the study Investigator prior to discharge. There was a minimum 5-day washout period between each dose of study drug.

Study Drugs

Intact Oxycodone DETERx® (Collegium Pharmaceutical, Inc., Canton, MA) and intact OxyContin® (Purdue Pharma, L.P., Stamford, CT) were administered as single 40 mg capsules and tablets, respectively, with 240 mL of non-carbonated, room temperature water.

Crushed Oxycodone DETERx® and crushed IR oxycodone (administered as 2 × 20 mg tablets; KVK-Tech, Inc., Newtown, PA) were prepared using the same method. Crushed OxyContin® was prepared using a different crushing method; however, in all cases, the most aggressive methods of reducing the particle size of the respective products was used based on data collected in previously conducted *in vitro* studies (Figure 1) [19]. The dosing procedure for crushed dosage forms was consistent across all three products in this study. Solid, crushed material was transferred in a dry state into the subject's mouth, followed by consumption of water. The dosing cups were then rinsed to ensure all crushed material had been transferred. Study staff conducted a visual oral cavity check to ensure that all study drug had been consumed.

Figure 1 (A) Oxycodone DETERx microspheres intact (1 × 40 mg); (B) Oxycodone DETERx microspheres crushed (1 × 40 mg); (C) OxyContin tablet intact (1 × 40 mg); (D) OxyContin tablets crushed (1 × 40 mg); (E) IR oxycodone intact (2 × 20 mg); (F) IR oxycodone crushed (2 × 20 mg). IR = immediate-release. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Pharmacokinetic Measures

During each Treatment Period, blood samples for determining plasma oxycodone concentrations were obtained for each subject just prior to dosing and at 0.25, 0.5, 0.75, 1.0, 1.25, 1.5, 1.75, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 6.0, 8.0, 12.0, 16.0, and 24.0 hours postdose for IR oxycodone and at 0.25, 0.5, 0.75, 1.0, 1.25, 1.5, 1.75, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0, 7.0, 8.0, 9.0, 10.0, 12.0, 24.0, and 36.0 hours postdose for intact and crushed Oxycodone DETERx® and intact and crushed OxyContin®. For each sample, approximately 3 mL of venous blood was collected. Plasma samples were analyzed using a LC-MS/MS method (Celerion, Lincoln, NE) to determine: area under the plasma concentration-time curve from time 0 to infinity (AUC_{INF}), area under the plasma concentration-time curve from time 0 to last measurable plasma concentration (AUC_{last}), maximum observed plasma concentration (C_{max}), time to reach maximum plasma concentration (T_{max}), partial area under the plasma concentration-time curve (PAUC) from time zero to all blood sample time points, and abuse quotient ($AQ = C_{max}/T_{max}$). The AQ takes into consideration a compound's maximum plasma concentration (C_{max}) and the time to reach that peak concentration (T_{max}). It is a measure of rate of rise in plasma concentration; the score is thought to be related to a product's abuse potential with a higher AQ indicating a steeper rise in plasma concentration and consequently a more desirable pharmacodynamic effect for an abuser [20]. Pharmacokinetic parameters were calculated from plasma concentration data using noncompartmental methods (WinNonlin Version 6.3, Pharsight Corporation, St. Louis, MO).

Safety Monitoring

Safety and tolerability evaluations included assessment of treatment-emergent adverse events (TEAEs), monitoring of vital signs, oxygen saturation, physical examinations, and results of clinical laboratory tests.

Pharmacokinetic and Statistical Analyses

Subjects who completed three of the five Treatment Periods, who had sufficient quantifiable plasma

Table 1 Mean oxycodone pharmacokinetic parameters

Parameter	Statistic	Crushed IR Oxycodone	Intact Oxycodone DETERx	Crushed Oxycodone DETERx	Intact OxyContin	Crushed OxyContin
	N	40	38	38	40	39
C_{max} (ng/mL)	Mean (SD)	79.4 (17.1)	67.5 (17.6)	62.9 (12.6)	64.9 (13.8)	78.4 (12.9)
T_{max} (hours)	Median (min–max)	1.75 (0.50–4.00)	3.50 (1.25–6.00)	4.00 (2.00–7.00)	5.00 (2.00–10.00)	1.75 (0.50–5.00)
$PAUC_{0-1.75\ h}$ (h*ng/mL)	Mean (SD)	87.1 (26.1)	12.9 (17.2)	23.4 (12.1)	14.5 (12.3)	81.4 (26.5)
AUC_{last} (h*ng/mL)	Mean (SD)	548 (140)	569 (139)	587 (151)	598 (146)	579 (130)
AUC_{inf} (h*ng/mL)	Mean (SD)	561 (146)	581 (138)	597 (149)	611 (145)	587 (132)
$t_{1/2}$ (hour)	Mean (SD)	4.25 (0.654)	5.74 (0.942)	5.00 (0.641)	4.29 (0.647)	4.49 (0.743)
AQ	Mean (SD)	62.3 (47.5)	20.9 (11.2)	16.5 (5.39)	14.0 (6.37)	58.1 (42.7)

AQ = abuse quotient; AUC_{inf} = area under the plasma concentration-time curve extrapolated to infinity; AUC_{last} = area under the plasma concentration time curve from 0 hours to the time of the last measurable plasma concentration; C_{max} = maximum observed plasma concentration; IR = immediate-release; Max = maximum; Min = minimum; PAUC = partial area under the plasma concentration-time curve; SD = standard deviation; $t_{1/2}$ = half-life; T_{max} = time to reach maximum plasma concentration.

concentration data to provide C_{max} and AUC data and who did not experience emesis within 12 hours of dosing were included in the pharmacokinetic analyses. Subjects who received at least one dose of study drug and for whom there was at least one post-treatment safety observation were included in the safety analyses.

For pharmacokinetic data, an analysis of variance was performed on the ln-transformed AUC_{last}, AUC_{INF}, and C_{max}. The model included sequence, treatment, and period as fixed effects, and subject nested within sequence as a random effect. Bioequivalence was concluded if the 90% confidence intervals (CIs) of the estimated mean ratios fell entirely within the 80.0–125% range (as per FDA guidance) [21]. The primary analyses were a comparison of crushed Oxycodone DETERx® vs crushed IR oxycodone, and crushed OxyContin® vs crushed IR oxycodone. Secondary analyses included comparisons of crushed Oxycodone DETERx® vs intact Oxycodone DETERx® and crushed OxyContin® vs intact OxyContin®; intact Oxycodone DETERx® vs crushed IR oxycodone and intact OxyContin® vs crushed IR oxycodone; and intact Oxycodone DETERx® vs intact OxyContin® and crushed Oxycodone DETERx® vs crushed OxyContin®.

Safety and tolerability were tabulated descriptively through TEAEs, vital signs measurements, oxygen saturation, and hematologic, biochemical, and urinalysis laboratory parameters.

Results

Subject Disposition and Demographics

Forty-two subjects (32 males and 10 females) were enrolled and randomized to receive study drug; 38 subjects (30 males and 8 females) completed the study. Four subjects were discontinued before completing the Treatment Phase (one subject discontinued because of a positive urine drug screen, one subject did not return to the clinic after Treatment Period 3 and was lost to follow-up, and two subjects were discontinued because they were unable to complete the HFHC meal). The mean (range) age of subjects was 37.7 (23–50) years. Subjects were mostly male (78.9%) and were either white (52.6%) or black/African American (47.4%).

Pharmacokinetics

After oral administration of crushed IR oxycodone with a HFHC meal, there was a rapid initial increase in mean plasma concentrations of oxycodone; C_{max} was reached at approximately 1.75 hours after dosing. Oral administration of crushed OxyContin® resulted in a similar rapid rise in plasma oxycodone concentrations with a similar C_{max} and T_{max} (Table 1) as the reference IR oxycodone product. In contrast, oral administration of both intact and crushed Oxycodone DETERx® resulted in a lower and delayed mean C_{max} (T_{max} 3.5 and 4.00 hours, respectively). The rise in plasma oxycodone concentrations was longest following administration of oral intact OxyContin®, with a mean C_{max} achieved at approximately 5 hours postdose (Figure 2). Although total plasma AUC values (AUC_{INF}) were similar between the different treatments (Table 1); cumulative PAUC values over 1.75 hours for crushed and intact Oxycodone DETERx® were much lower when compared with crushed IR oxycodone (Figure 2b).The cumulative PAUC values for intact OxyContin® were comparable to the values observed for intact and crushed Oxycodone DETERx®; however, the cumulative PAUC for crushed

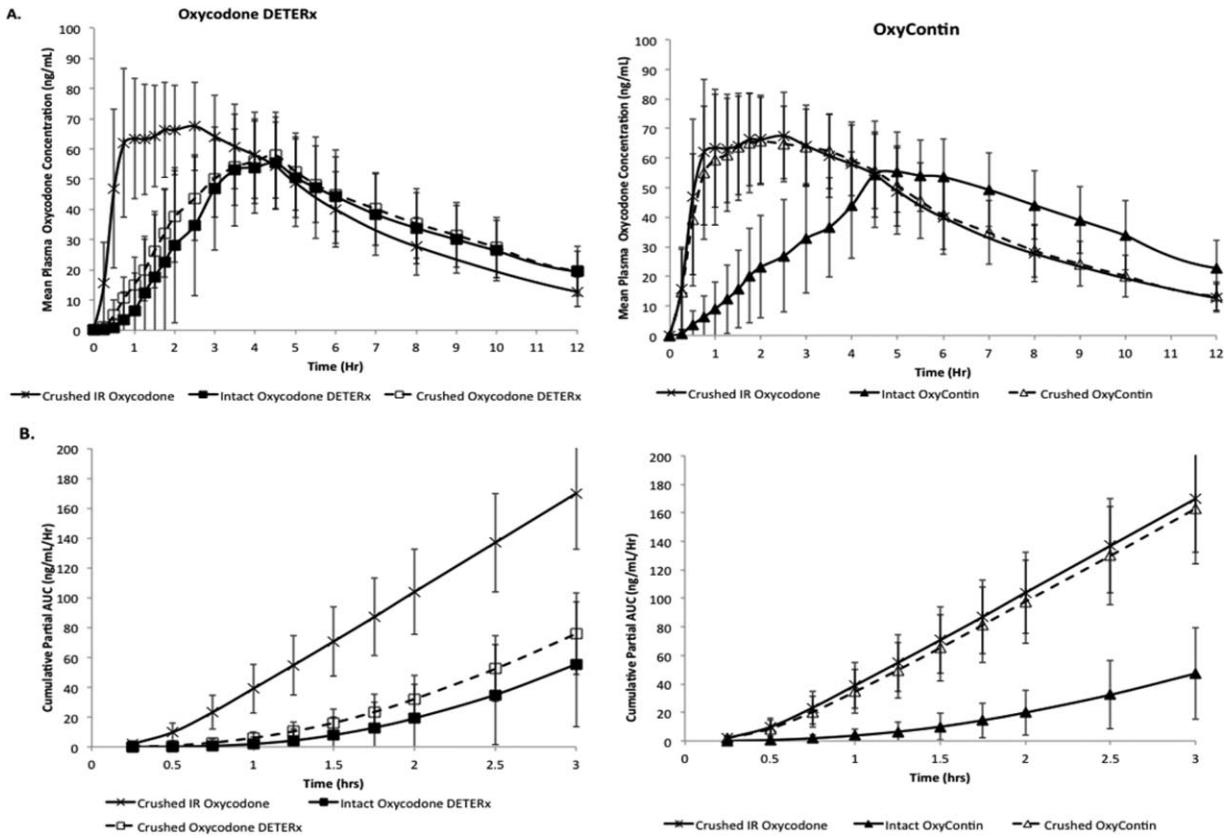

Figure 2 (A) Mean plasma concentration-time curve profiles compared with crushed IR oxycodone; (B) Cumulative partial area under the plasma concentration-time curve compared with crushed IR oxycodone. AUC = area under the plasma concentration-time curve; IR = immediate-release.

OxyContin® was similar to the values observed for crushed IR oxycodone (Figure 2b).

Statistical results of the comparisons between crushed and intact Oxycodone DETERx® and between both Oxycodone DETERx® doses and IR oxycodone are presented in Table 2. Crushed Oxycodone DETERx® had lower C_{max} and AUC_{INF} compared with crushed IR oxycodone; the two treatments were not bioequivalent. The median T_{max} was also significantly longer for crushed Oxycodone DETERx® compared with crushed IR oxycodone (median difference 2.0 hours, $P < 0.0001$). Peak (C_{max}) and total (AUC_{INF}) exposure to oxycodone was similar after oral administration of crushed and intact Oxycodone DETERx® with the CI and point estimates falling within the 80–125% CI range consistent with the bioequivalence criterion. The median difference in T_{max} between crushed Oxycodone DETERx® and intact Oxycodone DETERx® was 0.13 hours and was not statistically different ($P = 0.185$).

Crushed OxyContin® peak and total exposure was similar to crushed IR oxycodone; the two products were bioequivalent based on the CI and point estimates falling within the 80–1.25% range (Table 3). Crushed OxyContin® resulted in a substantially higher C_{max} compared with intact OxyContin®; as a result, the crushed and intact forms of OxyContin® were not bioequivalent on this measure, but were bioequivalent on AUC_{last} and AUC_{INF}. The median T_{max} for crushed OxyContin® did not differ from crushed IR oxycodone (1.75 hours) and was significantly shorter than intact OxyContin® (median difference 3.25 hours; $P < 0.0001$).

The highest mean AQ score was observed for crushed IR Oxycodone, followed closely by crushed OxyContin® (Table 1). In contrast, AQ values were markedly lower for intact and crushed Oxycodone DETERx® treatments as well as intact OxyContin®. Mean AQ value for crushed OxyContin® was approximately four-fold higher than that of intact OxyContin®. Likewise, the AQ value for crushed IR oxycodone was approximately three times greater than those of intact and crushed Oxycodone DETERx® (Figure 3).

Safety and Adverse Events

Single 40 mg oral doses of intact and crushed Oxycodone DETERx® following a HFHC meal and administered with 50 mg of naltrexone, were generally well-

Table 2 Results of treatment comparisons analysis: Oxycodone DETERx

	Crushed Oxycodone DETERx vs Intact Oxycodone DETERx		Crushed Oxycodone DETERx vs Crushed IR Oxycodone	
	LSMean ratio		LSMean ratio	
Parameter	(%)	90% CI	(%)	90% CI
C_{max} (ng/mL)	94.38	89.34, 99.71	77.41	73.50, 81.52
AUC_{inf} (h*ng/mL)	101.74	98.10, 105.51	103.68	100.59, 106.87

AUC_{inf} = area under the plasma concentration-time curve extrapolated to infinity; CI = confidence interval; C_{max} = maximum observed plasma concentration; IR = immediate-release; LSMean = least squares mean.

tolerated as were single doses of intact and crushed OxyContin® and crushed IR oxycodone.

The most common TEAEs (>5%) reported during this study were fatigue (5.3%) following administration of intact Oxycodone DETERx® and headache following administration of intact Oxycodone DETERx® (5.3%) and crushed IR oxycodone (7.5%). There were no TEAEs reported following administration of crushed or intact OxyContin® that were considered related to study drug. Most of the TEAEs reported were relatively transient and of mild to moderate intensity. None of the subjects experienced serious TEAEs and none of the subjects were discontinued from the study due to TEAEs. A summary of TEAEs by treatment is provided in Table 4. There were no clinically significant treatment-related changes in clinical laboratory results, vital signs, blood oxygen saturations levels or physical examination findings.

Discussion

The Oxycodone DETERx® formulation has been developed to provide physicians and patients with a novel ER oxycodone ADF without the use of aversive or antagonist agents. The purpose of this study was to evaluate the impact of tampering on the oral pharmacokinetics of the Oxycodone DETERx® capsule compared with an IR oxycodone and a currently marketed abuse-deterrent formulation of oxycodone, reformulated OxyContin®, in healthy, naltrexone blocked subjects using the most aggressive tampering method as determined from the results of *in vitro* manipulation studies [19].

Manipulation of Oxycodone DETERx® to its effective limit (i.e., "worst-case scenario") did not significantly change the oxycodone pharmacokinetic profile when compared with intact Oxycodone DETERx®; the crushed and intact products were bioequivalent with no significant difference in T_{max}. These results suggest that Oxycodone DETERx® had its intended effect of maintaining its ER characteristics despite tampering. Consistent with these findings, AQ values were comparable for crushed and intact Oxycodone DETERx® treatments, and were much lower compared with crushed IR oxycodone.

In contrast, crushing reformulated OxyContin® resulted in a significantly higher C_{max} and shorter median T_{max} compared with intact OxyContin®. Moreover, the early plasma exposure profile, as measured by cumulative PAUC up to 1.75 hours, was markedly different for crushed and intact OxyContin®; therefore, crushed OxyContin® was bioequivalent to crushed IR oxycodone, but not to intact OxyContin®. Although results of this study showed some minor differences in the pharmacokinetic profile between intact Oxycodone DETERx® and intact OxyContin®, the two products were bioequivalent on C_{max}, AUC_{last}, and $AUC_{INF.}$

The safety profile of crushed Oxycodone DETERx® was similar to that of intact Oxycodone DETERx®. Overall, all treatments were well-tolerated by study subjects, in part as a result of the naltrexone blockade, and none of the subjects withdrew from the study due to adverse events (AEs).

The goal of most abuse-deterrent opioid technologies is to make tampering more difficult or to make abuse of

Table 3 Results of treatment comparisons analysis: OxyContin

	Crushed OxyContin vs Intact OxyContin		Crushed OxyContin vs Crushed IR Oxycodone	
	LSMean ratio		LSMean ratio	
Parameter	(%)	90% CI	(%)	90% CI
C_{max} (ng/mL)	121.15	113.80, 128.98	101.69	95.80, 107.94
AUC_{inf} (h*ng/mL)	95.90	93.01, 98.89	106.44	98.96, 114.50

AUC_{inf} = area under the plasma concentration-time curve extrapolated to infinity; CI = confidence interval; C_{max} = maximum observed plasma concentration; IR = immediate-release; LSMean = least squares mean.

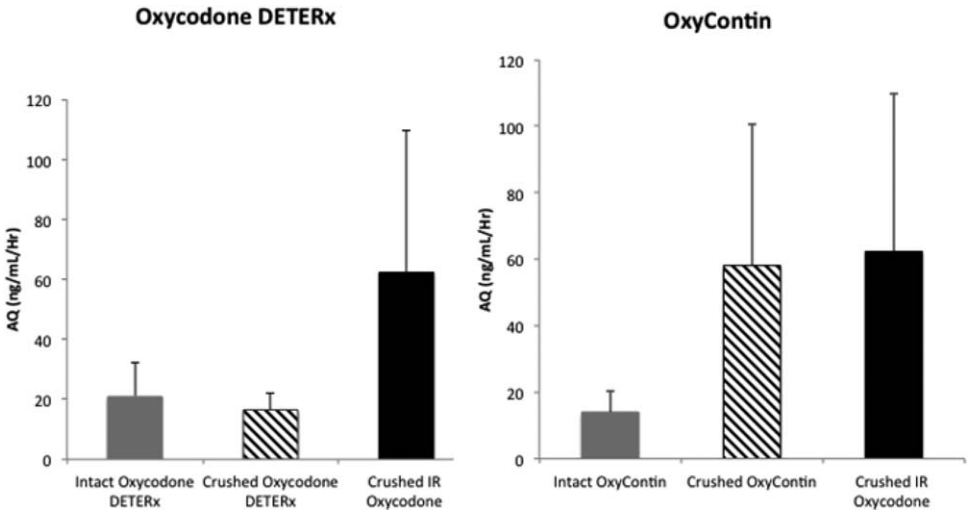

Figure 3 Mean abuse quotient value compared with crushed IR oxycodone. AQ = abuse quotient; IR = immediate-release.

the product via an unintended route (i.e., intranasal or intravenous) less attractive. For example, products with physicochemical deterrent properties are developed to be very hard or to contain excipients, which gel or clump when mixed with a liquid. Although these characteristics are useful in deterring abuse by the intranasal and intravenous routes, administration can be problematic in the intended patient population. For example, such tablets can be difficult to swallow due to the gelling components becoming sticky on contact with saliva. Many patients with pain, particularly those with dysphagia or odynophagia must consume their medication crushed and with food [22]. While it is possible to physically crush these hard, gelling tablets for oral administration, this practice significantly increases safety risks to patients and contain product warnings related to crushing. For example, the OxyContin® label states "cutting, breaking, chewing, crushing, or dissolving OxyContin® impairs the controlled-release delivery mechanism and results in the rapid release and absorption of a potentially fatal dose of oxycodone." This is also the case for agonist/antagonist ADFs such as those which contain a sequestered core of naltrexone (e.g., Embeda®), which, if administered crushed cannot only results in the treatment being ineffective, but can also elicit withdrawal in those patients who are physically dependent on opioids [23,24]. The current result, which found that crushed Oxycodone DETERx® was bioequivalent to intact Oxycodone DETERx® even when administered with food, supports the use of this product as a novel opioid-formulation for moderate to severe pain in patients who are unable to swallow solid, oral dosage forms.

Recent epidemiological research suggests that as more ADFs are approved and available to the public, illicit drug users are becoming more adept at defeating the deterrent properties of these formulations. The monitoring of public Internet forums revealed 37 "recipes" for circumventing the AD characteristics of one ADF ER opioid product, 32 of which were deemed feasible [25]. Therefore, from a public health perspective, there is an unmet need for a physicochemical ADF that, if defeated

Table 4 Subjects with TEAE with at least two subjects or two instances overall

	Crushed IR Oxycodone N = 40 N (%)	Intact Oxycodone DETERx N = 38 N (%)	Crushed Oxycodone DETERx N = 40 N (%)	Intact OxyContin N = 41 N (%)	Crushed OxyContin N = 39 N (%)
Any event	5 (12.5)	6 (15.8)	4 (10.0)	1 (2.4)	1 (2.6)
Nausea	1 (2.5)	0	0	1 (2.4)	0
Vomiting	1 (2.5)	0	0	1 (2.4)	0
Fatigue	0	2 (5.3)	1 (2.5)	0	0
Headache	3 (7.5)	2 (5.3)	1 (2.5)	0	0
Somnolence	0	0	2 (5.0)	0	0

The percentage is calculated on the basis of the number of subjects per treatment as the denominator. IR = immediate-release.

(i.e., crushed or chewed), still maintains its deterrent properties. Oxycodone DETERx® has been designed to retain its ER properties following manipulation and as a result deter illicit abuse. While it is still possible to abuse Oxycodone DETERx® orally by taking multiple capsules intact, it is likely that the ability to retain ER features following manipulation will make it less attractive to abusers compared with existing ADFs.

This study was conducted in line with the FDA guidance recommendations for assessing the pharmacokinetic profile of an abuse deterrent product [26], including the inclusion of a reference product (IR oxycodone) and an active comparator (OxyContin®), and the inclusion of extensive blood sampling time points to appropriately characterize the pharmacokinetic profile when a product is then administered intact and crushed. This study design did not include an assessment of the subjective effects (e.g., "drug-liking" or "desire to take the drug again") of Oxycodone DETERx® when administered intact and crushed. Subjective measures, particularly the assessment of "at-this-moment'" drug-liking, are considered the most sensitive and face-valid measures of abuse potential [27,28]. Therefore, a HAL study was recently conducted to investigate whether the maintenance of ER properties in physically manipulated Oxycodone DETERx® will be sufficient to decrease the positive subjective effects in recreational drug users.

Conclusions

These data demonstrate that on physical manipulation crushed Oxycodone DETERx® retains its ER profile in contrast to crushed reformulated OxyContin® ADF, which showed a similar pharmacokinetic profile as crushed IR oxycodone when administered orally. These results suggest that the Oxycodone DETERx® formulation may be less attractive to illicit drug users compared with existing ADFs, while also providing a novel extended release treatment option for pain patients who have painful or difficulty with swallowing.

References

1 Cheung CW, Qiu Q, Choi SW, et al. Chronic opioid therapy for chronic non-cancer pain: A review and comparison of treatment guidelines. Pain Physician 2014;17:401–14.

2 Franklin GM. Opioids for chronic noncancer pain: A position paper of the American academy of neurology. Neurology 2014;83:1277–84.

3 Katz NP, Sherburne S, Beach M, et al. Behavioral monitoring and urine toxicology testing in patients receiving long-term opioid therapy. Anesth Analg 2003;97:1097–102.

4 Rosenblum A, Marsch LA, Joseph H, Portenoy RK. Opioids and the treatment of chronic pain: Controversies, current status, and future directions. Exp Clin Psychopharmacol 2008;16:405–16.

5 Trescot AM, Helm S, Hansen H, et al. Opioids in the management of chronic non-cancer pain: An update of American society of the interventional pain physicians' (ASIPP) guidelines. Pain Physician 2008;11:S5–6.

6 Substance Abuse and Mental Health Services Administration, National Survey on Drug Use and Health: Summary of National Findings (NSDUH). 2002–2013. Past Month Illicit Drug Use among Persons Aged 12 or Older. 2014.

7 Substance Abuse and Mental Health Services Administration, Drug Abuse Warning Network, 2011: National Estimates of Drug-Related Emergency Department Visits. HHS Publication No. (SMA) 13-4760, DAWN Series D-39. Rockville, MD: Substance Abuse and Mental Health Services Administration; 2013.

8 Dart RC, Surratt HL, Cicero TJ, et al. Trends in opioid analgesic abuse and mortality in the United States. N Engl J Med 2015;372(3):241–8.

9 Larochelle MR, Zhang F, Ross-Degnan D, Wharam JF. Rates of opioid dispensing and overdose after introduction of abuse-deterrent extended-release oxycodone and withdrawal of propoxyphene. JAMA Intern Med 2015;In Press

10 McCarberg BH, Barkin RL. Long-acting opioids for chronic pain: Pharmacotherapeutic opportunities to enhance compliance, quality of life, and analgesia. Am J Ther 2001;8:181–6.

11 Nicholson B. Benefits of extended-release opioid analgesic formulations in the treatment of chronic pain. Pain Pract 2009;9:71–81.

12 Comer SD, Ashworth JB, Sullivan MA, et al. Relationship between rate of infusion and reinforcing strength of oxycodone in humans. J Opioid Manag 2009;5:203–12.

13 Hays L, Kirsh KL, Passik SD. Seeking drug treatment for OxyContin abuse: A chart review of consecutive admissions to a substance abuse treatment facility in Kentucky. J Natl Compr Canc Netw 2003;1:423–8.

14 Raffa RB, Pergolizzi JV Jr. Opioid formulations designed to resist/deter abuse. Drugs 2010;70:1657–75.

15 Romach MK, Schoedel KA, Sellers EM. Update on tamper-resistant drug formulations. Drug Alcohol Depend 2013;130:13–23.

16 Schaeffer T. Abuse-deterrent formulations, an evolving technology against the abuse and misuse of opioid analgesics. J Med Toxicol 2012;8:400–7.

17 Pergolizzi JV Jr, Taylor R Jr, Nalamachu S, et al. Challenges of treating patients with chronic pain with dysphagia (CPD): Physician and patient perspectives. Curr Med Res Opin 2014;30:191–202.

18 Perrino PJ, Colucci SV, Apseloff G, Harris SC. Pharmacokinetics, tolerability, and safety of intranasal administration of reformulated OxyContin® tablets compared with original OxyContin® tablets in healthy adults. Clin Drug Investig 2013;33:441–9.

19 Kopecky EA, Fleming AB, Noonan PK, et al. Impact of physical manipulation on in vitro and in vivo release profiles of oxycodone DETERx®: An extended-release, abuse-deterrent formulation. J Opioid Manag 2014;10:227–40.

20 Webster L. The question of opioid euphoria. drug discovery and development. Available at: http://www.dddmag.com/articles/2009/07/question-opioid-euphoria (accessed 11 November 2014).

21 CDER Guidance for Industry: Food-Effect Bioavailability and Fed Bioequivalence Studies. Silver Spring, MD: Food and Drug Administration; December 2002.

22 Argoff CE, Kopecky EA. Patients with chronic pain and dysphagia (CPD): Unmet medical needs and pharmacologic treatment options. Curr Med Res Opin 2014;30:2543–59.

23 Ruan X, Chen T, Gudin J, Couch JP, Chiravuri S. Acute opioid withdrawal precipitated by ingestion of crushed embeda (morphine extended release with sequestered naltrexone): Case report and the focused review of the literature. J Opioid Manag 2010;6:300–3.

24 Badalamenti VC, Buckley JW, Smith ET. Safety of EMBEda (morphine sulfate and naltrexone hydrochloride) extended-release capsules: Review of postmarketing adverse events during the first year. J Opioid Manag 2012;8:115–25.

25 McNaughton EC, Coplan PM, Black RA, et al. Monitoring of internet forums to evaluate reactions to the introduction of reformulated OxyContin to deter abuse. J Med Internet Res 2014;16(5):e119.

26 CDER Guidance for Industry: Guidance for Industry: Abuse-Deterrent Opioids—Evaluation and Labeling. Silver Spring, MD: US Food and Drug Administration; 2013.

27 Balster RL, Bigelow GE. Guidelines and methodological reviews concerning drug abuse liability assessment. Drug Alcohol Depend 2003;70:S13–40.

28 Griffiths RR, Bigelow GE, Ator NA. Principles of initial experimental drug abuse liability assessment in humans. Drug Alcohol Depend 2003;70(3 Suppl):S41–54.