ORIGINAL RESEARCH ARTICLE

Pharmacokinetics, Tolerability, and Safety of Intranasal Administration of Reformulated OxyContin® Tablets Compared with Original OxyContin® Tablets in Healthy Adults

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Abstract

Background and Objective Reformulated OxyContin® (oxycodone-HCl controlled release) tablets (ORF) became available in the United States in August 2010. The original formulation of OxyContin® (oxycodone-HCl controlled release) tablets (OC) used a delivery system that did not provide inherent resistance to crushing and dissolving. The objective of this study was to compare the pharmacokinetics, tolerability, and safety of finely crushed ORF tablets, coarsely crushed ORF tablets, and finely crushed OC tablets.

Methods This randomized, single-blind, single-dose, single-center, six-sequence, triple-treatment, triple-period crossover study enrolled eligible healthy adults (aged 18–55 years inclusive). The study evaluated the pharmacokinetics, tolerability, and safety of intranasally administered ORF, both finely crushed and coarsely crushed, as well as finely crushed OC tablets. Plasma oxycodone concentrations were quantified and analyzed to determine the maximum observed plasma concentration (C_{max}), time to maximum plasma concentration (t_{max}), area under the plasma concentration–time curve from hour 0 to the last measurable plasma concentration (AUC_{last}), and area under the plasma concentration–time curve extrapolated to infinity (AUC_∞). The abuse quotient (AQ), calculated as C_{max}/t_{max}, served as an index of the average rate of increase in drug concentration from dosing to t_{max}. Intranasal tolerability rating scales (discomfort, itching, burning, pain, runny nose, and stuffiness) and intranasal endoscopy were conducted. Safety assessments included adverse events, vital signs, pulse oximetry (SpO_2), and electrocardiograms.

Results Of 83 subjects screened and enrolled, 30 were randomized to period 1, with 1 subject subsequently discontinuing due to the subject's choice. Mean C_{max} values for finely crushed ORF (17.1 ng/mL) and coarsely crushed ORF (15.5 ng/mL) were lower than that for finely crushed OC (22.2 ng/mL). Median t_{max} for finely crushed OC (1.0 h) was shorter than that for either finely crushed ORF (2.0 h) or coarsely crushed ORF (3.0 h). Mean AQ values were approximately 66 and 80 % lower, respectively, for finely crushed ORF and coarsely crushed ORF than that for finely crushed OC. Finely crushed ORF, coarsely crushed ORF, and finely crushed OC demonstrated similar total oxycodone exposures (AUC_∞). Insufflation of ORF produced greater nasal discomfort and stuffiness than finely crushed OC, although the latter produced higher runny nose scores. No significant difference was found in other nasal tolerability measures. The overall safety profile was as expected following opioid administration in healthy subjects.

Conclusions In contrast to OC, both finely and coarsely crushed ORF retained some control of oxycodone release. Reduced C_{max} and increased t_{max} for ORF resulted in lower AQ scores for ORF compared with OC. ORF was associated with greater intranasal irritation than OC. These data suggest that ORF has a lower intranasal abuse potential than OC.

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1 Introduction

Opioid analgesic utilization for pain management has increased significantly since 1998; unfortunately, along with the increase in the legitimate use of opioid

medications, there has also been an escalation in the abuse of prescription opioids, particularly abuse of controlled-release formulations that contain higher opioid content [1, 2]. Compared with substances such as cocaine and heroin, prescription opioids are relatively easier to obtain and are perceived as more socially acceptable to abuse. They have also been mentioned as possible "gateway" drugs to other illegal substances [3–5].

Experienced abusers and recreational users commonly employ alternate routes of administration (e.g., injecting and snorting) in abusing oral opioid medications [4, 6, 7]. Data suggest that the incidence of injecting oral oxycodone products among these experienced and recreational abusers ranges from 22 to 59 %, and the incidence of intranasal administration ranges from 45 to 92 % [6, 7]. Abuse via these routes first requires tampering to accelerate the release of the active opioid, which rapidly provides a high blood concentration compared with oral delivery [8]. To reduce abuse and misuse, particularly by injecting and snorting oral opioid analgesics, pharmaceutical manufacturers have begun to develop tamper-deterrent products [2].

Reformulated OxyContin® (oxycodone-HCl controlled release; ORF) was developed with the specific intent of reducing abuse and misuse of the original formulation of OxyContin® (OC) without affecting legitimate use for the management of pain. ORF tablets became available in the United States in August 2010 at the same time that shipments of OC were discontinued. OC used a delivery system that did not provide inherent resistance to breaking, crushing, and dissolving. ORF was designed to be orally bioequivalent to OC, but with abuse-deterrent properties that make abuse via nonoral routes of delivery more difficult. During formulation development, laboratory-based tamper testing indicated that, when crushed, ORF tablets fractionate into large pieces that discourage intranasal abuse, and when dissolved in small amounts of aqueous solution, the particles form a viscous solution that discourages intravenous abuse [9].

This study focuses on intranasal administration of oxycodone, because it is associated with faster absorption than oral administration and may therefore pose a greater risk to the abuser [10]. Additionally, intranasal administration involves crushing or pulverizing the tablets, which may compromise their controlled-release properties. It was hypothesized that upon intranasal administration, the tamper-deterrent properties of ORF relative to OC would translate into a reduction in maximum observed plasma concentration (C_{max}), an increase in time to maximum plasma concentration (t_{max}), and a corresponding decrease in the abuse quotient (AQ) [6, 11, 12], suggestive of a decrease in abuse potential.

The objective of this study was to compare the pharmacokinetics, tolerability, and safety of finely crushed ORF tablets, coarsely crushed ORF tablets, and finely crushed OC tablets, each intranasally administered as single 10-mg doses.

2 Methods

2.1 Study Design

This was a randomized, single-blind, single-dose, single-center, six-sequence, triple-treatment, triple-period crossover study designed to evaluate the pharmacokinetics, tolerability, and safety of intranasally administered ORF, both finely crushed (10 mg) and coarsely crushed (10 mg), as well as finely crushed OC (10 mg). Coarsely crushed OC was not tested because simple crushing of OC readily produces a fine powder. To minimize variability, tampered tablets were prepared using standardized equipment and techniques.

Study duration was up to 42 days; a 28-day screening phase was followed by a 7-day treatment phase, with follow-up 3–7 days after the last dose of study drug. The treatment phase was divided into three periods (days 1–3, 3–5, and 5–7). The assignment of subjects to treatment sequence was single-blinded. Efforts were made to prevent subjects from making side-by-side comparisons of study drugs, which were similar, but not identical, in appearance.

This study protocol and its informed consent form was submitted to the Western Institutional Review Board (IRB) for review and approval. It was conducted in accordance with regulatory guidelines and the applicable International Conference on Harmonization guidelines of Good Clinical Practice, as consistent with the Declaration of Helsinki. All subjects provided oral and written consent before conduct of any protocol-related procedures. Subjects were informed that they could discontinue the study at any time.

2.2 Subjects

Subjects were healthy men and women (aged 18–55 years inclusive) with no clinically significant medical history or any other concerns that would have jeopardized the study's safety or validity, as determined by the principal investigator. Special preference for study enrollment was given to recreational drug users who had experience with opioid use on at least five occasions, and to subjects who reported at least three occasions of intranasal opioid use for the purpose of abuse/misuse within the past year. Subjects were excluded if they had significant obstruction of either naris, or clinically important changes in the intranasal cavity that would interfere with the study procedures or data integrity or compromised the safety of the subject. Subjects with piercings through the nose or a perforated nasal septum

were given a lower priority than those without these findings.

Other conditions warranting exclusion from participation were use of any medication/herbal product [except paracetamol (acetaminophen) (2 g/day), vitamin or mineral supplements, birth control, and hormone replacement] within 7 days of study drug administration or for the study duration.

2.3 Treatment

A physical examination, biochemistry tests, and urinalysis were conducted for each subject at screening. Subjects abstained from consuming alcoholic beverages for 48 h prior to initial study drug administration (day 1) and for the duration of the study (i.e., through to the end of study procedures). They were confined to a nonsmoking study facility the day prior to administration of the study drug and throughout all three periods of the study. Subjects abstained from caffeine or xanthine entirely during confinement. While confined at the study site, they received meals at scheduled times that did not conflict with other study-related activities. The same standard meal timing was employed over corresponding study days in each period, but the content of meals varied.

Subjects were randomized to a treatment sequence on the morning of day 1 and received treatments on days 1, 3, and 5 of the treatment phase, with a minimum washout period of 48 h between dose administrations. For each treatment period, subjects completed a 10-h overnight fast before sitting in an upright position and intranasally insufflating a dose of finely crushed ORF (10 mg), coarsely crushed ORF (10 mg), or finely crushed OC (10 mg) through a short thin straw. Dosing was carefully observed by the site staff, and the weight of any drug not successfully insufflated during the 5-min administration period was recorded, with significant amounts of nonadministered drug potentially resulting in subject discontinuation from the study. Subjects continued fasting for 4 h subsequent to dosing and were to remain upright, unless a procedure required that they be in the supine position. They remained confined to the study site throughout all three treatment periods and abstained from strenuous exercise or physical exertion. Treatment procedures were identical for all three treatment periods, with subjects receiving single intranasal doses of study drug in alternating nares (e.g., left-right-left). Telephone follow-ups were conducted 3–7 days after the last dose or following early discontinuation.

2.4 Pharmacokinetic Measures

During each treatment period, blood samples for determining oxycodone plasma concentrations were obtained for each subject just prior to dosing and at 0.25, 0.5, 0.75, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 5.0, 6.0, 8.0, 10, 12, 16, 24, 28, 32, 36, and 48 h postdose. For each sample, venous blood (4 mL) was drawn via an indwelling catheter or direct venipuncture into tubes containing potassium ethylenediaminetetraacetic acid anticoagulant. A validated liquid chromatography tandem mass spectrometric method quantified plasma concentrations of oxycodone (lower limit of quantitation was 0.1 ng/mL).

Relative bioavailability was determined by comparison to the reference treatment (finely crushed OC). Pharmacokinetic metrics were calculated, whenever possible, based on the plasma concentrations of oxycodone according to the model independent approach. Pharmacokinetic calculations were performed using WinNonLin (Pharsight Corporation, St. Louis, MO, USA; Version 5.2). Noncompartmental analysis of plasma oxycodone concentrations generated values for: maximum observed plasma concentration (C_{max}), time to maximum plasma concentration (t_{max}), area under the plasma concentration–time curve from hour 0 to the last measurable plasma concentration (AUC_{last}), area under the plasma concentration–time curve extrapolated to infinity (AUC_∞), and half-life ($t_{1/2}$). These pharmacokinetic metrics permit assessment of the rate and extent of drug absorption (bioavailability). AUC_∞ is an index of total drug exposure and C_{max} is an index of maximum or peak exposure to treatment. The AQ, calculated as C_{max}/t_{max}, is a measure of the average rate of rise in concentration between dosing and t_{max} [12]. Because more rapid exposure to higher opioid concentrations correlates with greater drug-liking, higher AQ scores predict greater abuse potential [6, 11, 12].

2.5 Intranasal Tolerability

Pharmacodynamic measurements were assessed by evaluating intranasal tolerability. Subjects rated intranasal discomfort, itching, burning, pain, runny nose, and stuffiness on numeric scales ranging from 0 (none) to 10 (worst I can imagine). Ratings measured only the naris used for drug administration. Intranasal tolerability rating scales were evaluated at predose and at 0.25, 0.5, 0.75, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 5.0, 6.0, 8.0, 10, and 12 h postdose. At approximately 5 and 24 h after each dosing, subjects provided a written response to the question, "What effects (if any) did snorting this drug cause to the inside of your nose?" Additionally, a specialist in ear, nose, and throat procedures performed intranasal endoscopies. These were conducted at predose, and as close to 0.5 h postdose as possible, but not later than 2 h postdose.

2.6 Safety Measures

Safety assessments included reports of adverse events (AEs), clinical laboratory test results, vital signs results,

pulse oximetry (SpO_2), physical examinations, and electrocardiograms (ECGs). Reported AEs were coded according to the *Medical Dictionary for Regulatory Activities* (version 9.1) by preferred term and system organ class. AEs reported herein are those that emerged, reemerged, and/or worsened in severity during treatment and were classified as treatment-emergent AEs.

2.7 Statistical Analysis

Subjects who were randomized, received study drug, and had at least one postdose safety assessment were included in safety analyses; subjects who were randomized, received study drug, and had at least one valid pharmacokinetic metric were included in pharmacokinetic analyses. For pharmacokinetic data, a mixed-model analysis of variance was used to compare logarithmic-transformed (base *e*) values for C_{max}, AUC_{last}, and AUC_∞ of oxycodone, with fixed effects for treatment, period, and sequence, as well as random effects of subject within sequence.

For pharmacokinetic data, bioequivalence was indicated if the 90 % confidence intervals (CIs) for oxycodone for a given measure fell entirely within the 80–125 % range. Intranasal tolerability rating scales used descriptive statistics for raw data and for differences from predose for each time point and treatment. The maximum response over time was tabulated and an analysis of covariance model was conducted to assess differences among treatments related to maximum response. This pharmacodynamic model included a covariate for the predose assessment, fixed effects for treatment, period, and sequence, and a random effect of the subject within sequence.

3 Results

Of 83 subjects screened and enrolled, 30 were randomized (Fig. 1). One was discontinued in period 1 due to the subject's choice, leaving 29 in treatment periods 2 and 3. The mean (range) age of subjects was 32 (19–52) years. Of the randomized subjects, most were male (66.7 %) and most were white (83.3 %). Mean (range) body weight, height, and body mass index were 78.1 (49.9–94.0) kg, 171.5 (156.0–187.0) cm, and 26.5 (19.1–31.9) kg/m^2, respectively.

3.1 Pharmacokinetics

After intranasal administration, mean C_{max} was lower for finely crushed ORF and coarsely crushed ORF than that for finely crushed OC (Table 1; Fig. 2). The mean C_{max} metric ratio comparing coarsely crushed ORF and finely crushed OC indicated a 33 % lower C_{max} for coarsely crushed ORF
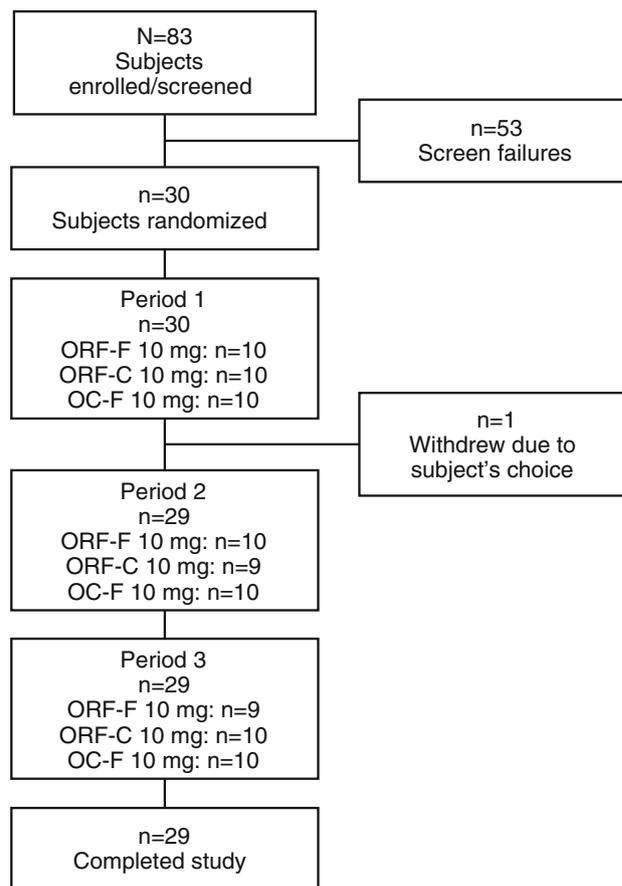
Fig. 1 Study disposition. *OC-F* finely crushed original formulation of oxycodone-HCl controlled release, *ORF-C* coarsely crushed reformulated oxycodone-HCl controlled release, *ORF-F* finely crushed reformulated oxycodone-HCl controlled release

(Table 2). The mean C_{max} metric ratio comparing finely crushed ORF and finely crushed OC indicated a 22 % lower C_{max} for finely crushed ORF. In addition, median t_{max} values were reached more rapidly for finely crushed OC than for either finely crushed ORF or coarsely crushed ORF (Table 1; Fig. 2). The highest mean AQ score was observed for finely crushed OC (31.7 ng/mL per h) compared with either ORF preparation (Fig. 3), with mean AQ scores for finely crushed ORF and coarsely crushed ORF approximately 66 and 80 % lower, respectively, versus finely crushed OC.

After intranasal administration, mean oxycodone AUC_∞ values were 124, 134, and 128 ng·h/mL for finely crushed ORF, coarsely crushed ORF, and finely crushed OC, respectively (Table 1). Mean metric ratios between finely crushed ORF, coarsely crushed ORF, and finely crushed OC are illustrated in Table 2. With mean metric ratios falling within the 80–125 % CI range for all treatment comparisons, these results indicated comparability of treatments for average total oxycodone exposure.

Table 1 Mean oxycodone pharmacokinetic metrics (full analysis population)

Parameter		ORF-F 10 mg (n = 29)	ORF-C 10 mg (n = 29)	OC-F 10 mg (n = 30)
C_{max} (ng/mL)	Mean (SD)	17.1 (3.65)	15.5 (5.41)	22.2 (4.87)
AUC_∞ (ng·h/mL)	Mean (SD)	124 (29.3)	134 (45.1)	128 (29.4)
AUC_{last} (ng·h/mL)	Mean (SD)	123 (29.2)	133 (45.0)	127 (29.4)
t_{max} (h)	Median (range)	2.00 (0.75–3.50)	3.00 (1.00–8.13)	1.00 (0.25–2.50)
$t_{1/2}$ (h)	Mean (SD)	4.43 (0.786)	4.45 (0.796)	4.46 (0.810)

AUC_∞ area under the plasma concentration–time curve extrapolated to infinity, AUC_{last} area under the plasma concentration–time curve from hour 0 to the last measurable plasma concentration, C_{max} maximum observed plasma concentration, *OC-F* finely crushed original formulation of oxycodone-HCl controlled release, *ORF-C* coarsely crushed reformulated oxycodone-HCl controlled release, *ORF-F* finely crushed reformulated oxycodone-HCl controlled release, *SD* standard deviation, $t_{1/2}$ half-life, t_{max} time to maximum plasma concentration
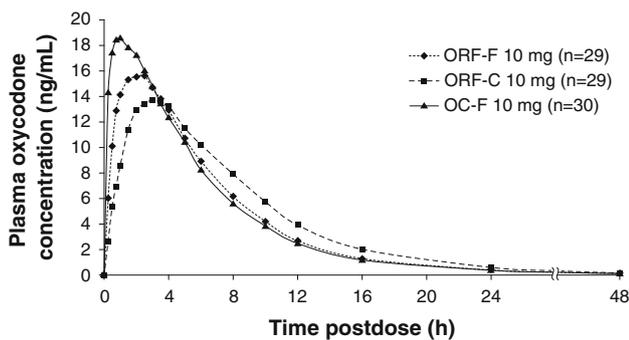
Fig. 2 Mean plasma oxycodone concentrations following intranasal dosing over time in the full analysis set. *OC-F* finely crushed original formulation of oxycodone-HCl controlled release, *ORF-C* coarsely crushed reformulated oxycodone-HCl controlled release, *ORF-F* finely crushed reformulated oxycodone-HCl controlled release

3.2 Intranasal Tolerability

Compared with finely crushed OC, insufflation of finely crushed ORF and coarsely crushed ORF produced significantly higher mean ratings of nasal discomfort ($P = 0.0030$ and $P < 0.0001$, respectively) and intranasal stuffiness ($P < 0.0001$ for each) (Fig. 4). Insufflation of finely crushed ORF produced a significantly lower mean rating for runny nose than finely crushed OC ($P = 0.0363$), and coarsely crushed ORF yielded significantly greater intranasal discomfort than finely crushed ORF ($P = 0.0106$). There were no significant differences noted for other measures of nasal tolerability (burning, itching, or pain).

Intranasal endoscopy at 0.5 h after insufflation of either ORF preparation revealed a coarse, white, gel-foam-type material in the nasal passages of subjects, whereas nasal passages were clear after insufflation of finely crushed OC. Subject comments corroborated these findings (see representative data in Fig. 5).

3.3 Safety

No deaths or serious adverse events were reported. Of the 93 AEs reported, 25 were reported in 15 subjects with finely crushed ORF, 29 were reported in 12 subjects with coarsely crushed ORF, and 39 were reported in 9 subjects with finely crushed OC. One subject chose to discontinue from the study due to an AE of nausea with finely crushed OC (10 mg) dosing. The most commonly reported AEs were headache, nausea, and vomiting and most AEs were of mild or moderate severity. The number and percentage of distinct subjects with AEs that were judged to be related to study treatment are shown in Table 3. All AEs resolved by study end. The eight AEs that were severe and related to treatment were vomiting (3), nausea (3), headache (1), and pain in extremity (1); these were reported by four subjects. Results of laboratory tests, vital signs measurements, SpO_2 evaluations, and ECG recordings revealed no clinically significant abnormalities and raised no safety concerns for the study treatments.

4 Discussion

This study compared the effects of original OxyContin® (OC) and reformulated OxyContin® (ORF) on the pharmacokinetic, pharmacodynamic, and safety profiles of healthy men and women. ORF, with its abuse-deterrent properties of reduced crushability showed the intended effects of reduced C_{max}, delayed t_{max}, reduced AQ, and significantly increased intranasal intolerability compared with OC. The safety profile of ORF was similar to that of OC. Most AEs for all treatments were classified as mild or moderate and were those commonly associated with opioid use (e.g., nausea, vomiting, and headache).

Subjects reported greater intranasal discomfort, stuffiness, and intranasal obstruction with ORF than with OC. Decreased subject-reported tolerability and visual demonstrations of increased deposition of undissolved, crushed ORF suggest that recreational abusers, intent on using intranasal administration of prescription opioids, may find that ORF has low desirability. The current study examines acute tolerability of a single-dose administration, so the

Table 2 Treatment comparisons of pharmacokinetic metrics

Parameter		ORF-C vs ORF-F	ORF-F vs OC-F	ORF-C vs OC-F
C_{max} (ng/mL)	Mean ratio of PK metric (90 % CI)	86.3 (76.91, 96.78)	77.6 (69.27, 87.02)	67.0 (59.76, 75.07)
AUC_∞ (ng·h/mL)	Mean ratio of PK metric (90 % CI)	103.0 (91.64, 116.10)	97.4 (86.56, 109.50)	100.0 (89.29, 112.94)

Treatment groups were ORF-C 10 mg ($n = 29$), ORF-F ($n = 29$), and OC-F 10 mg ($n = 30$)

AUC_∞ area under the plasma concentration-time curve extrapolated to infinity; *CI* confidence interval, C_{max} maximum observed plasma concentration, *OC-F* finely crushed original formulation of oxycodone HCl controlled release, *ORF-C* coarsely crushed reformulated oxycodone HCl controlled release, *ORF-F* finely crushed reformulated oxycodone HCl controlled release, *PK* pharmacokinetic

Parameter	ORF-F 10 mg (n=29)	ORF-C 10 mg (n=29)	OC-F 10 mg (n=30)
Abuse quotient, ng/mL/h [mean (SD)]	10.7 (7.22)	6.4 (4.54)	31.7 (25.90)
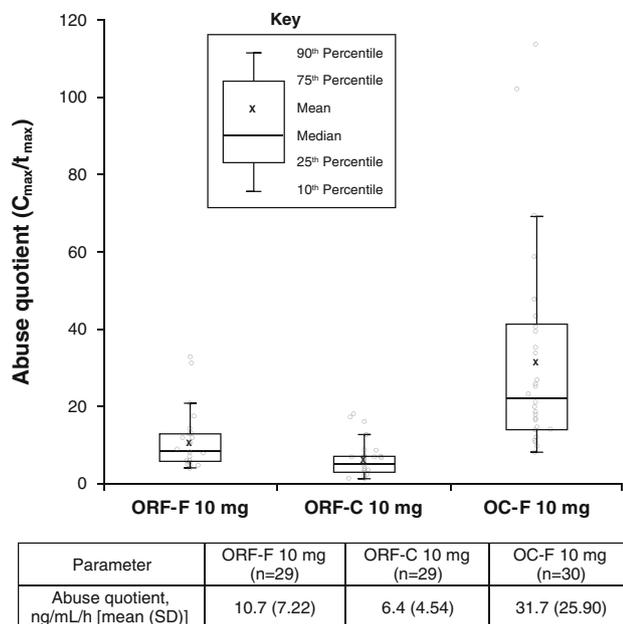
Fig. 3 Abuse quotient box and whisker plots. The *open circles* represent the individual abuse quotient values for each patient. C_{max} maximum observed plasma concentration, *OC-F* finely crushed original formulation of oxycodone-HCl controlled release, *ORF-C* coarsely crushed reformulated oxycodone-HCl controlled release, *ORF-F* finely crushed reformulated oxycodone-HCl controlled release, *SD* standard deviation, t_{max} time to maximum plasma concentration

impact of chronic intranasal abuse of ORF cannot be determined. However, medical complications involving the nasal mucosa with chronic intranasal substance abuse have been documented [13–15].

This study focused on OxyContin® abuse via the intranasal route of administration (i.e., snorting), which is a commonly used method of abuse [7]. OC can be easily crushed to disable its controlled-release properties [6, 8, 16, 17]. The pharmacokinetic profile of orally administered, crushed OC has been shown to be similar to that of immediate-release oxycodone [18]. In addition, intranasal administration of crushed OC resulted in rapid absorption, with most (approximately 75 %) of the administered dose being absorbed, indicating that intranasal administration after crushing is an efficient means of defeating the controlled-release properties of original OxyContin® [8]. This

is not unexpected given evidence showing the nasal mucosa is an efficient absorptive surface for agents delivered in powdered form [19, 20]. The rapid rate of absorption that occurs with intranasal nonmedical administration of opioids may increase their abuse potential. Furthermore, recent findings suggest that rate of infusion of opioids, including intravenous morphine [21] and oxycodone [22], is an important determinant of the reinforcing effects of these agents, with rapid infusion resulting in greater effects.

The ultimate goal of the development of ORF was to replace a readily abusable product with an abuse-deterrent product that reduced the frequency and adverse consequences of abuse while maintaining access to treatment for patients with moderate to severe pain who require a continuous, around-the-clock opioid analgesic for an extended period of time. Although no opioid product can ever be abuse-proof [1, 2], abuse-deterrent products offer the possibility of incremental or more substantial reductions in abuse potential compared with previously developed products that are more easily altered, depending upon the product/formulation, the route, the tampering method, and the population [2].

The current study, illustrating the differences in pharmacokinetic profile of intranasal administration of OC and ORF, includes elements that have been recommended for assessing the pharmacokinetic profile of an abuse-deterrent product [3, 23]. Pharmacokinetic and safety analyses are one of four critical components used to characterize the abuse potential of ORF. The other components consist of in vitro tamper-testing studies conducted during formulation development [9], abuse-liking studies [24, 25], and, lastly, epidemiological studies. The real-world impact of any abuse-deterrent product needs to be established by a variety of epidemiologic studies conducted in real-world settings [1–3, 11, 12]. Those epidemiologic studies are currently in progress for reformulated OxyContin® [26]. Recently reported findings appear to support the laboratory-based tamper-testing and abuse potential studies for ORF, including decreased rates of self-reported nonoral abuse in a large national interview survey database [27]; decreased rates of intranasal abuse in a cohort of OxyContin® abusers in rural Kentucky [28]; and decreased incidence of diversion and a decrease in reported street value in surveys from law enforcement agencies [29, 30].
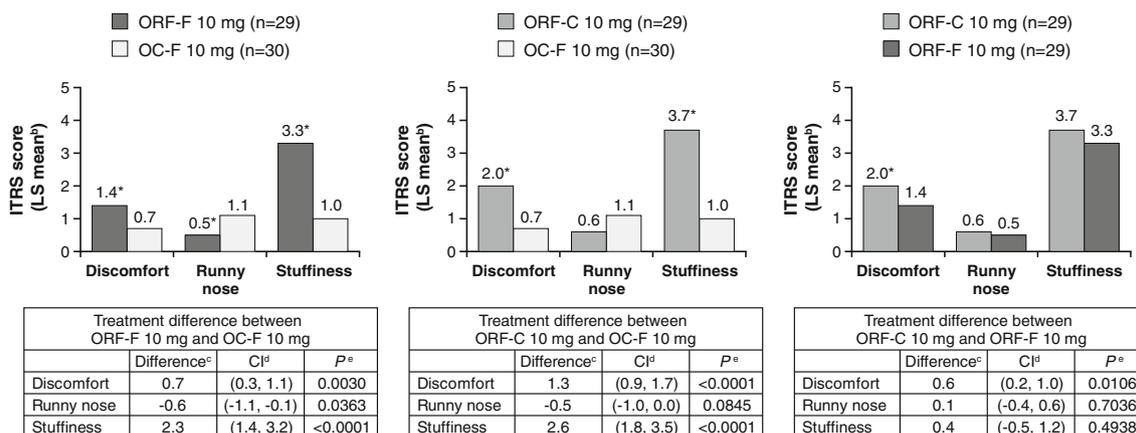
Fig. 4 Comparison of maximum response over time on the Intranasal Tolerability Rating Scale (ITRS[a]) in the randomized safety population. [a]ITRS was rated on an 11-point scale, ranging from 0 (none) to 10 (worst I can imagine). [b]LS means from ANCOVA. [c]Difference of means between treatments from ANCOVA. [d]90 % CI for difference of means from ANCOVA. [e]P value for pairwise comparison between treatments from ANCOVA. *P < 0.05 between treatment groups. *ANCOVA* analysis of covariance, *CI* confidence interval, *ITRS* Intranasal Tolerability Rating Scale: ITRS was rated on an 11-point scale, ranging from 0 (none) to 10 (worst I can imagine), *LS* least squares, *OC-F* finely crushed original formulation of oxycodone-HCl controlled release, *ORF-C* coarsely crushed reformulated oxycodone-HCl controlled release, *ORF-F* finely crushed reformulated oxycodone-HCl controlled release
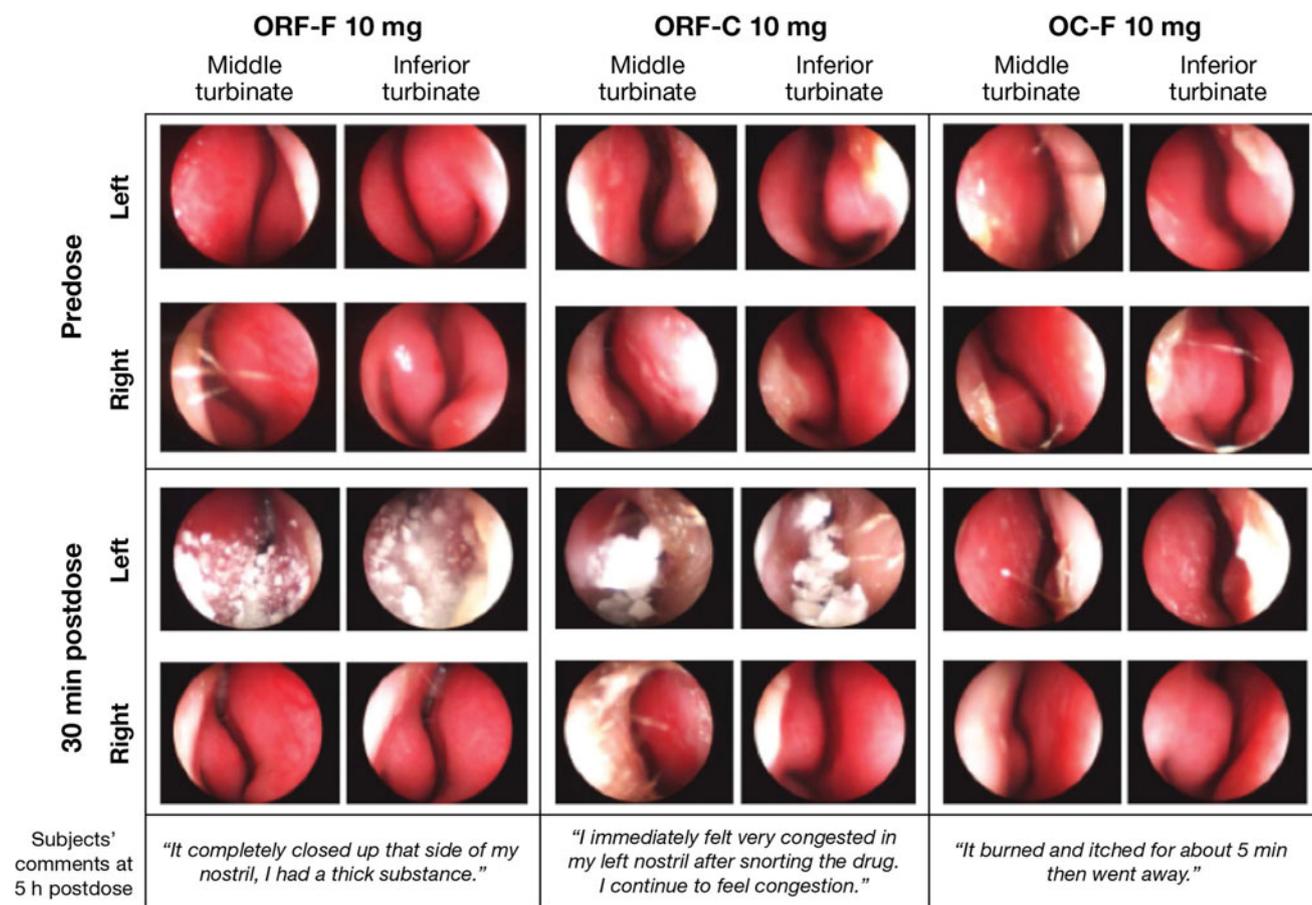
Fig. 5 Representative intranasal endoscopy results. *OC-F* finely crushed original formulation of oxycodone-HCl controlled release, *ORF-C* coarsely crushed reformulated oxycodone-HCl controlled release, *ORF-F* finely crushed reformulated oxycodone-HCl controlled release

Table 3 Subjects with treatment-emergent adverse events with at least two subjects or two instances overall in the randomized safety population

AE, MedDRA-preferred term	ORF-F 10 mg (n = 29) n (%)			ORF-C 10 mg (n = 29) n (%)			OC-F 10 mg (n = 30) n (%)			Overall n = 30
	Mild	Moderate	Severe	Mild	Moderate	Severe	Mild	Moderate	Severe	
Dizziness	0	1 (3.4)	0	1 (3.4)	0	0	1 (3.3)	0	0	3 (10.0)
Dry throat	0	0	0	0	2 (6.9)	0	0	0	0	2 (6.7)
Headache	3 (10.3)	2 (6.9)	0	1 (3.4)	5 (17.2)	0	2 (6.7)	3 (10.0)	1 (3.3)	10 (33.3)
Nausea	5 (17.2)	3 (10.3)	1 (3.4)	6 (20.7)	1 (3.4)	0	2 (6.7)	3 (10.0)	2 (6.7)	10 (33.3)
Pharyngolaryngeal pain	0	0	0	0	0	0	1 (3.3)	1 (3.3)	0	2 (6.7)
Presyncope	0	0	0	0	0	0	0	2 (6.7)	0	2 (6.7)
Vomiting	2 (6.9)	0	1 (3.4)	3 (10.3)	1 (3.4)	0	2 (6.7)	4 (13.3)	2 (6.7)	6 (20.0)

AE adverse event, *MedDRA* Medical Dictionary for Regulatory Activities, version 9.1, *OC-F* finely crushed original formulation of oxycodone HCl controlled release, *ORF-C* coarsely crushed reformulated oxycodone HCl controlled release, *ORF-F* finely crushed reformulated oxycodone HCl controlled release

One limitation of the present study is that statistical significance testing using *P* values was not done. Another limitation is that the endpoints were for pharmacokinetics and safety only, and standardized measures of "drug liking" were not incorporated. The results of the present study can be more clearly interpreted in light of subsequent research looking at both pharmacokinetics and the pharmacodynamics of drug liking.

In January 2013, the US Food and Drug Administration (FDA) released its guidance, *Abuse-Deterrence Opioids—Evaluation and Labeling* [31]. This guidance proposes that summary statements and label claims regarding abuse deterrence can be based on pharmacokinetic data. The present study employed the major design elements recommended by the FDA in this guidance: the use of the most common route of administration for abuse, the impact of food and alcohol taken into consideration in the design of the study, the measurement of the rate of rise of drug concentration, the inclusion of relevant pharmacokinetic parameters, and the documenting of AEs.

5 Conclusions

In contrast to the original formulation, reformulated OxyContin® administered intranasally demonstrated a lower C_{max}, a longer t_{max}, and a lower AQ when compared with the original formulation. Crushed reformulated OxyContin® was also associated with greater intranasal irritation than crushed original OxyContin®, with otherwise similar safety profiles. Overall, these data suggest that reformulated OxyContin® has a reduced abuse potential compared to the original formulation upon intranasal administration.

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