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Abuse Potential, Pharmacokinetics, Pharmacodynamics, and Safety of Intranasally Administered Crushed Oxycodone HCl Abuse-Deterrent Controlled-Release Tablets in Recreational Opioid Users

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Abstract

The objective of this study was to evaluate abuse potential, pharmacokinetics, pharmacodynamics, and safety of intranasally administered, crushed reformulated OxyContin® (oxycodone HCl controlled-release) tablets (ORF), relative to crushed original OxyContin® (OC), oxycodone powder (Oxy API), and OC placebo. This randomized, double-blind, positive- and placebo-controlled crossover study enrolled healthy, adult, nonphysically dependent recreational opioid users with recent history of intranasal drug abuse (N = 27). Active treatments contained oxycodone (30 mg). Pharmacokinetics, pharmacodynamics (e.g., Overall Drug Liking [ODL], Take Drug Again [TDA], and High Visual Analog Scales [VAS]; Subjective Drug Value [SDV]; pupillometry; intranasal irritation), and safety (e.g., adverse events, vital signs, laboratory tests) were assessed to 24 hours postdose. Crushed ORF administration yielded reduced oxycodone C_{max} and increased T_{max} versus crushed OC and Oxy API. Peak effects for pharmacodynamic measures were delayed with ORF (1–2 hours) versus OC and Oxy API (0.5–1 hour). ODL, TDA, High VAS, and SDV E_{max} values were significantly lower ($P \leq .05$) and some intranasal irritation ratings were greater for ORF versus OC and Oxy API. No significant or unexpected safety findings were observed. Compared with OC and Oxy API, intranasally administered ORF was associated with lower and delayed peak plasma concentrations, decreased drug-liking, and decreased intranasal tolerability. This suggests that ORF has a decreased potential for intranasal oxycodone abuse. There were no significant or unexpected safety findings. As is true for all abuse potential studies, epidemiological or other appropriate post-marketing studies are required to assess the impact of the reduction in intranasal oxycodone abuse potential observed in the present study on real-world patterns of ORF misuse, abuse, and diversion.

The direct and indirect costs of chronic pain in the United States have been estimated at more than $100 billion annually in medical expenses, lost wages, and lost productivity.[1] Prescription opioids are an important treatment option for the management of chronic pain, but their misuse and abuse constitute a substantial medical and public health problem.[2]

While opioids are often abused via intact oral administration, opioid dosage forms are also frequently tampered with and then abused orally or via alternate routes of administration (predominantly intranasal and intravenous routes) that provide rapid opioid delivery to the central nervous system.[3–5] In an effort to reduce abuse via alternate routes, opioid formulations have been created with features designed to deter tampering, such as physical barriers (e.g., excipients that resist manipulation) and inclusion of antagonists (e.g., naloxone or naltrexone) that block opioid effects.[6] It is recognized that no opioid formulation is immune to tampering by knowledgeable drug abusers,[6] but tamper-deterrent formulations may serve to decrease the public health burden of opioid abuse

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by making abuse more difficult, more time consuming, and less effective to the abuser.

The original formulation of OxyContin® (OC) was approved in 1995 by the Food and Drug Administration (FDA) for use in the treatment of moderate to severe pain. The original formulation provided no inherent resistance to tampering, and the control of oxycodone release could be easily defeated by crushing the tablet into a fine powder. By 2001, OC had been identified as one component of the growing problem of prescription drug abuse.[7–9] The FDA responded to this problem, in part, by working with industry to develop proactive risk mitigation strategies. Such strategies for OC included adding a black box warning to product labelling and initiating a proactive surveillance progam for prescription opioid abuse and diversion.[7]

To further address the problem of misuse, abuse, and diversion of OC, an abuse-deterrent reformulation of OxyContin® (ORF) was developed. ORF was designed to be bioequivalent to OC following intact oral administration and to resist physical and chemical manipulations intended to defeat the control of oxycodone release. In vitro tampering studies demonstrated that ORF resists crushing and other particle size reduction efforts. ORF is anticipated to discourage tampering and intranasal oxycodone abuse. Firstly, tampering with ORF requires significant time and effort. Secondly, the particles produced by tampering with ORF may retain some controlled-release properties. Thirdly, the size of the particles may serve to increase both the likelihood of incomplete dosing and the severity of nasal irritation associated with insufflation. Lastly, when ORF is dissolved in small volumes for intravenous administration, it forms a viscous solution that cannot be effectively drawn into a syringe.[10] However, since ORF is designed to deliver oxycodone over time when taken as directed, it can be abused by taking intact tablets orally without legitimate purpose.

This study of recreational opioid users evaluated the abuse potential, pharmacokinetics, pharmacodynamics, and safety of finely and coarsely crushed, intranasally administered ORF tablets relative to finely crushed OC, oxycodone powder (Oxy API), and OC placebo. It examined intranasal administration (i.e., snorting) of crushed ORF and OC for three reasons: because intranasal administration has been found to be a route preferred among abusers for delivery of opioids, including oxycodone[5,11] and OC specifically[12]; because intranasal administration involves the crushing or pulverizing of ORF, which may compromise its controlled-release properties[13]; and because the accelerated absorption afforded by intranasal administration may pose a greater risk to the abuser.

ORF is the only available controlled-release formula of oxycodone at present. Other products are in development by other companies, but none are currently approved or commercially available. The results of this study apply strictly to ORF.

Methods

Ethical Conduct
This study was conducted at INC Research Toronto Inc., Toronto, Canada, in accordance with the Declaration of Helsinki and its amendments as outlined by the International Conference on Harmonisation. Prior to study initiation, the Institutional Review Board, IRB Services, Aurora, Canada, approved informed consent forms and the study protocol in accordance with Good Clinical Practice and applicable regulatory requirements.

Subjects
The study enrolled eligible healthy male and female adults (aged 18–55 years, inclusive) who reported a history of nonmedical use of opioids via the intranasal route, though reports of other routes of administration did not preclude participation. The absence of opioid physical dependence was assessed by interview and confirmed by the results of a naloxone challenge. Subjects were excluded if they had an Objective Opiate Withdrawal Scale (OOWS)[14] score 3 or greater following the naloxone challenge test, self-reported drug dependence (past 2 years), or a positive urine drug screen or breath alcohol test. Key restrictions included abstaining from alcohol consumption for 48 hours prior to each visit and from recreational drug use from screening through study completion. Also not permitted were caffeine consumption for 24 hours prior to clinic admission and nicotine consumption from 11 PM the night before until 8 hours after each dose administration.

Overall Study Design
This was a randomized, double-blind, positive- and placebo-controlled, five-treatment crossover study that evaluated the abuse potential, pharmacodynamics, pharmacokinetics, and safety profile of finely and coarsely crushed ORF versus OC and Oxy API according to current guidelines for studies of abuse liability.[15,16] The study consisted of: a screening phase, a qualification phase, a treatment phase, and a follow-up visit (2–4 days following the last treatment visit or after early withdrawal). The screening phase included a naloxone challenge to determine physical dependence.

In the qualification phase, subjects self-administered intranasal doses of 30-mg Oxy API and volume-matched lactose powder placebo in a randomized crossover fashion, with approximately 24 hours between administrations. Subjects were eligible to enter the double-blind treatment phase if they tolerated 30-mg Oxy API. Additionally, the fulfillment of one of the following three criteria was required: (1) subjects had both a peak score

for lactose powder placebo ≤ 55 on a 0–100 point bipolar Drug Liking visual analog scale (VAS) where 50 represented a "neutral" response, *AND* a peak score ≤ 10 on the unipolar 0–100 High VAS where 0 represented a "no effects" response; *OR* (2) subjects had both a peak Drug Liking VAS score for 30-mg Oxy API powder greater than OC placebo by at least 15 points *AND* a peak High VAS score greater than OC placebo by at least 30 points. Finally, subjects were eligible to enter the treatment phase if their responses to Oxy API and OC placebo were judged to be acceptable by the investigator on VAS for Drug Liking, Good Effects, Bad Effects, and High.

In the double-blind treatment phase, subjects self-administered intranasal doses of the five study treatments in a randomized crossover fashion, with a washout period of at least 48 hours between treatments. The five treatments were lactose powder OC placebo, 30-mg finely crushed ORF, 30-mg coarsely crushed ORF, 30-mg finely crushed OC, and 30-mg Oxy API powder. Coarsely crushed OC was not tested because simple crushing of OC readily produces a fine powder. OC placebo consisted of finely ground OC placebo tablets that were prepared in the same manner as the active OC tablets.

Pharmacokinetic Assessments

Plasma oxycodone concentrations were quantified from venous blood samples collected via an indwelling cannula or by direct venipuncture at predose, and at 0.25, 0.5, 1, 2, 3, 4, 6, 8, and 24 hours postdose. A solid-phase extraction method was used to extract oxycodone from 200 μL plasma samples. The extracted samples were analyzed by LC-MS/MS using a Phenomenex Luna Si, 5 μm, 2 mm × 100 mm, normal phase column. The mobile phase used was 85:15 (0.1% formic acid in acetonitrile:0.2% formic acid in 20 mM ammonium formate buffer, v/v). The mass spectrometer was operated in the multiple reaction monitoring (MRM) mode with positive ion detection. The lower limit of quantitation (LOQ) for oxycodone was 0.1 ng/mL.

Pharmacodynamic Assessments

The various computer-administered "100-point" VAS used to evaluate the drug administration experience are detailed in Table 1, which also includes timepoints of VAS assessments. Subjective Drug Value (SDV) was administered at 8 and 24 hours postdose. Pupillometry was assessed predose and 0.5, 1, 2, 3, 4, 6, and 8 hours postdose. Subjects were instructed to base their responses

Table 1. Bipolar and Unipolar Visual Analog Scales

VAS	Type	0–100 VAS		
		0	50	100
Drug Liking[a]	Bipolar	At this moment, my liking for this drug is:		
		Strong Disliking	Neutral	Strong Liking
Overall Drug Liking[b]		Overall, my liking for this drug is:		
		Strong Disliking	Neutral	Strong Liking
Take Drug Again[b]		I would take this drug again:		
		Definitely Not	Neutral	Definitely So
Alertness/Drowsiness[c]		I am feeling:		
		Very Drowsy	Neutral	Very Alert
High[c]	Unipolar	I am feeling high:		
		Definitely Not		Definitely So
Good Effects[a]		I can feel good drug effects:		
		Definitely Not		Definitely So
Bad Effects[a]		I can feel bad drug effects:		
		Definitely Not		Definitely So
Any Effects[a]		I can feel any drug effect:		
		Definitely Not		Definitely So

VAS, visual analog scale. Subjects completed VAS endpoints via computer by using the mouse to position a cursor at the appropriate place on each scale and clicking "OK."
[a]Administered at 0.5, 1, 2, 3, 4, 6, 8, and 24 hours postdose.
[b]Administered at 8 and 24 hours postdose.
[c]Administered predose and at 0.5, 1, 2, 3, 4, 6, 8, and 24 hours postdose.

on cumulative or overall assessment of drug effects for Overall Drug Liking VAS, Take Drug Again VAS, and SDV. For other VAS, subjects based their responses on effects "at this moment."

The SDV assessment involved a series of independent, hypothetical forced choices between the study drug administered and different monetary amounts. Subjects were asked to choose between receiving another dose of the same drug to take home or an envelope containing a specified amount of money ($0.25–$50.00). Subjects did not receive either the study drug or the money described in the choices. This test was adapted from a similar procedure extensively utilized by Griffiths et al.[17,18]

Pupillometry[19] and intranasal photography served as two additional measures of pharmacologic and physicochemical effects. An ear, nose, and throat specialist assessed intranasal irritation using endoscopy and intranasal photography. Intranasal irritation was assessed after observing the subject for at least 3 minutes. Subject rated assessment of intranasal irritation (SRAII) assessed five categories (burning, need to blow nose, runny nose/nasal discharge, facial pain/pressure, and nasal congestion) on the same 6-point scale: 0 = not observed/no problem; 1 = very mild problem; 2 = mild/slight problem; 3 = moderate problem; 4 = severe problem; or 5 = very severe problem/"as bad as can be."

In a post-hoc analysis, each individual study subject was assessed for percent reduction in Drug Liking VAS between OC and ORF. A similar analysis assessed percent reduction in Drug Liking VAS between Oxy API powder and ORF.

Safety Assessments

Safety assessments consisted of adverse events (AEs), vital signs, laboratory assessments, and 12-lead electrocardiogram (ECG). AE reports and vital signs were collected from the time of the signing of the informed consent form through to the end of the follow-up phase. Laboratory assessments and ECG readings were completed during screening, at admission to each treatment phase visit, and at follow-up.

Statistical Analysis

Pharmacokinetic analyses were conducted on the pharmacokinetic population (i.e., all subjects who were randomized, received active study drug, and had at least one valid pharmacokinetic metric). Pharmacokinetic parameters were derived using noncompartmental methods. Pharmacokinetic metrics were: maximum plasma concentration (C_{max}), time to maximum plasma concentration (T_{max}), area under the concentration time curve from time zero to infinity (AUC_{inf}), and terminal half-life ($t_{1/2}$). Abuse quotient ($AQ = C_{max}/T_{max}$), a measure of the average rate of increase in plasma oxycodone concentra-

tion over the interval between treatment administration and the time of maximum oxycodone concentration, was also calculated.[5,20]

Abuse quotients were calculated as a post hoc analysis using general linear model with treatment and subject as independent variables. Pairwise comparisons of treatments were performed.

Mean scores for maximum and minimum effect (E_{max} and E_{min}) were derived for Drug Liking VAS; mean E_{max} and E_{min} were also measured at 8 and 24 hours for Overall Drug Liking VAS, Take Drug Again VAS, and SDV. E_{max} was derived for High VAS, Good Effects VAS, and SRAII. E_{min} was derived for pupillometry. Time to E_{min} and time to E_{max} were also calculated for VAS and pupillometry measures. Pharmacodynamic derived parameters were analyzed using a mixed-effect model for a crossover study. The model included treatment, period, sequence, and first-order carryover effects as fixed effects, baseline (predose) measurements as covariate, where appropriate, and subject nested within treatment sequence as a random effect. For the purposes of study validation, as assessed by comparison of Oxy API versus OC placebo and OC versus OC placebo, the primary pharmacodynamic endpoints were E_{max} of Drug Liking VAS, Overall Drug Liking VAS, and SDV. However, relative abuse potential conclusions were based on responses on all pharmacodynamic measures.

Safety analyses were conducted on the safety population (i.e., all subjects who took at least one dose of study drug in the treatment phase).

Results

Disposition and Demographic Data

Thirty subjects met qualification criteria and were randomized to the treatment phase. Of these, three subsequently withdrew from the study. Therefore, 27 met all protocol-specific procedures and assessments and were designated as study completers.

Subjects were predominantly male (86.7%) and white (86.7%). The mean (standard deviation [SD]) age was 32.1 (8.99) years, with a range of 18–48 years, and the body mass index ranged from 19.0 to 29.7 kg/m². All subjects reported a history of recreational opioid use (codeine, dihydrocodeine, heroin, hydromorphone, morphine, opium, OxyContin, oxycodone, oxycodone-acetaminophen, acetaminophen-codeine). Recreational use of other psychoactive drugs was reported by 86.7% of subjects for cannabinoids (hashish, marijuana), 53.3.% for stimulants (amphetamines, cocaine, MDMA), 30.0% for depressants (benzodiazepines, lorazepam, alprazolam), 30.0% for dissociative anesthetics (ketamine), and 23.3% for hallucinogens (LSD, psychedelic mushrooms).
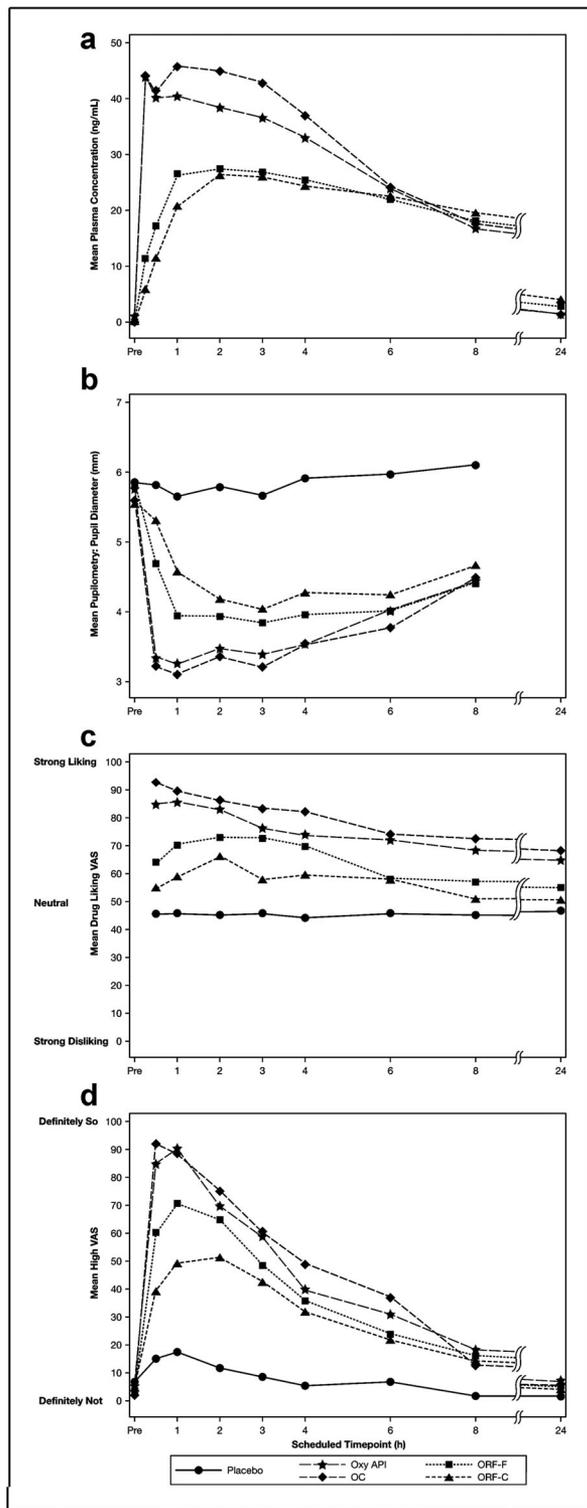
Figure I. (a–d) Time course of pharmacokinetic and pharmacodynamic effects. (a) Mean plasma oxycodone concentration over time (pharmacokinetic population). (b) Mean pupil size over time (pharmacodynamic population). (c) Mean Drug Liking VAS over time ("at this moment, my liking for this drug is") (pharmacodynamic population). (d) Mean High VAS over time ("I am feeling high...") (pharmacodynamic population). h, hour; OC, finely crushed OC; ORF-C, coarsely crushed ORF; ORF-F, finely crushed ORF; Oxy API, oxycodone powder; VAS, Visual Analog Scale. *Pupillometry was collected for 8 hours after dosing.

Pharmacokinetics

Dosing. Incomplete dosing occurred in 9/28 subjects receiving ORF-C (32%), 10/29 subjects receiving ORF-F (34%), 2/28 subjects receiving OC (7%), 0/29 subjects receiving Oxy API, and 3/29 subjects receiving OC placebo (10%).

Pharmacokinetic Parameters. Figure 1a illustrates mean plasma oxycodone concentrations over time, and Table 2 summarizes derived pharmacokinetic parameters by active treatment. C_{max} values were lower for finely and coarsely crushed ORF than for OC and Oxy API. Median T_{max} values for finely and coarsely crushed ORF were approximately twice as long as those observed for OC and Oxy API. Mean AUC_{inf} values were comparable across all active treatments. Median $t_{1/2}$ values were somewhat higher and more variable for finely and coarsely crushed ORF compared with that of OC and Oxy API.

AQ. Abuse quotients were fivefold higher for Oxy API and OC (102.15 and 94.75 ng/mL/h, respectively) compared with finely and coarsely crushed ORF (17.57 and 16.96 ng/mL/h, respectively). AQ for finely and coarsely crushed ORF were significantly lower ($P < .0001$) than crushed Oxy API and OC.

Pharmacodynamics

Across all subjective pharmacodynamic measures, responses were largest for the positive controls, smallest for OC placebo, and intermediate for finely and coarsely crushed ORF, with finely crushed ORF generally showing larger responses than coarsely crushed ORF. The larger responses seen for the positive control treatment supported the validity of the study design.

Pupillometry. Intranasal administration of Oxy API and OC resulted in oxycodone-induced miosis (i.e., reduced pupil size) that peaked at 0.5–1 hour postdose versus OC placebo. Mean pupil size then increased slightly beginning at 3 hours postdose (Figure 1b). No notable differences in peak scores were observed between positive control treatments. E_{min} values for Oxy API and OC were significantly lower than OC placebo ($P < .001$ for each). Compared with positive control treatment, ORF administration showed a more gradual onset in pupil-size reduction, peaking at approximately 2–3 hours postdose. Mean E_{min} values were significantly lower for both finely and coarsely crushed ORF compared with that for Oxy API and OC and significantly higher than that for OC placebo ($P < .001$ for all comparisons). No notable differences were observed in pupil-size scores across time with OC placebo treatment.

Subjective Effects

Qualification phase. During the qualification phase, subjects demonstrated the ability to distinguish between Oxy API and OC placebo treatments. Mean (SD) E_{max} values for Oxy API and OC placebo, respectively, were, for the primary measures: 94.3 (11.0) and 45.1 (18.6) for

Table 2. Pharmacokinetic and Pharmacodynamic Parameters (Pharmacokinetic and Pharmacodynamic Populations)

	ORF-F	ORF-C	OC	Oxy API
Pharmacokinetic parameters				
C_{max} (ng/mL)				
Mean (SD)	29.4 (7.71)	29.8 (12.2)	59.6 (16.2)	52.1 (13.0)
Geometric Mean (%CV)	28.4 (26.2)	27.0 (51.0)	57.5 (28.3)	50.6 (25.0)
T_{max} (h)				
Median (range)	2.08 (1.07–6.07)	2.62 (0.25–8.1)	1.10 (0.25–3.13)	1.00 (0.25–4.10)
AUC_{inf} (ng/mL/h)				
Mean (SD)	339 (101)	376 (182)	385 (102)	350 (69.6)
Geometric mean (%CV)	323 (33.8)	320 (74.1)	372 (27.5)	343 (20.6)
$t_{1/2}$ (h)				
Median (range)	5.6 (3.4–12.1)	6.6 (4.1–12.5)	4.2 (3.18–7.1)	4.07 (3.39–5.99)
AQ				
Mean (SD)	17.57 (9.59)	16.96 (19.66)	94.75 (91.87)	102.15 (95.73)

	ORF-F	ORF-C	OC	Oxy API	OC Placebo
Pharmacodynamic parameters					
Overall Drug Liking VAS ("Overall, my liking for this drug is…")					
E_{max}					
Mean (SD)	69.7 (29.4)	61.1 (25.8)	87.4 (22.2)	84.8 (18.9)	48.9 (14.8)
Take Drug Again VAS					
E_{max}					
Mean (SD)	64.0 (38.2)	52.8 (37.4)	89.6 (20.7)	86.6 (23.5)	28.2 (24.3)
Subjective Drug Value					
E_{max}					
Mean (SD)	$17.01 ($16.39)	$17.25 ($17.93)	$27.95 ($16.03)	$27.30 ($17.40)	$0.37 ($0.60)

AUC_{inf}, area under the concentration time curve from time zero to infinity; AQ, abuse quotient (i.e., C_{max}/T_{max}); C_{max}, maximum plasma concentration; CV, coefficient of variation; E_{max}, maximum effect; OC, finely crushed OC; ORF-C, coarsely crushed ORF; ORF-F, finely crushed ORF; Oxy API, oxycodone powder; SDV, Subjective Drug Value; T_{max}, time to maximum plasma concentration; $t_{1/2}$, terminal elimination half life; VAS, visual analog scale.

Drug Liking VAS; 90.0 (16.30) and 41.0 (19.24) for Overall Drug Liking VAS; and $30.90 ($16.40) and $0.25 ($0) for SDV.

Treatment Phase. For both Drug Liking and High VAS, E_{max} responses were highest for the positive controls, and these occurred within 1 hour postdose (Figure 1c,d). The positive controls showed comparable peak scores and time courses. Lower peak responses were seen with both finely and coarsely crushed ORF, and these occurred later than for the positive controls. Responses for the positive controls and for ORF were all higher than for OC placebo. The peak response and time course of coarsely crushed ORF were lower than for finely crushed ORF.

For Overall Drug Liking VAS, Take Drug Again VAS, and SDV, responses remained relatively consistent at 8 and 24 hours postdose (Table 3). The highest responses were seen for the positive controls, the lowest response was seen for OC placebo, and intermediate responses were seen for finely and coarsely crushed ORF, with coarsely crushed ORF showing lower responses than finely crushed ORF.

Table 2 presents mean (SD) E_{max} values for Overall Drug Liking VAS, Take Drug Again VAS, and SDV. All

Table 3. Overall Subjective Drug Effects (Pharmacodynamic Population)

Pharmacodynamic measure	N	8 hours mean (SD)	24 hours mean (SD)
Overall Drug Liking VAS			
Oxy API	29	81.9 (23.71)	82.7 (19.54)
OC	28	84.0 (23.26)	84.6 (23.41)
ORF-F	29	66.0 (31.87)	63.3 (30.23)
ORF-C	28	58.1 (28.23)	54.9 (28.57)
OC placebo	29	44.9 (16.39)	47.7 (14.90)
Take Drug Again VAS			
Oxy API	29	84.7 (23.52)	84.4 (24.80)
OC	28	86.4 (22.93)	87.4 (23.89)
ORF-F	29	59.8 (40.41)	55.9 (36.84)
ORF-C	28	49.6 (37.83)	47.7 (37.31)
OC placebo	29	26.7 (24.70)	26.6 (24.95)
Subjective Drug Value			
Oxy API	29	$25.61 ($18.15)	$26.22 ($17.65)
OC	28	$23.83 ($17.08)	$26.61 ($16.32)
ORF-F	29	$13.59 ($15.37)	$15.34 ($16.28)
ORF-C	28	$14.55 ($16.72)	$15.55 ($18.24)
OC placebo	29	$0.37 ($0.60)	$0.25 ($0.0)

OC, finely crushed OC; ORF-C, coarsely crushed ORF; ORF-F, finely crushed ORF; Oxy API, oxycodone powder.

active treatments had E_{max} values that were significantly greater versus OC placebo ($P \leq .003$) except coarsely crushed ORF, which did not differ from OC placebo on Overall Drug Liking ($P = .07$). Finely and coarsely crushed ORF had significantly lower E_{max} values versus positive controls for all three global measures of drug effect ($P \leq .002$). E_{max} values for finely and coarsely crushed ORF did not differ significantly from each other on Take Drug Again VAS and SDV. The E_{max} value for Overall Drug Liking VAS was significantly lower for coarsely crushed versus finely crushed ORF ($P = .043$). Similarly, OC and Oxy API were associated with mean (SD) SDV E_{max} of $27.95 (16.03) and $27.30 (17.40), respectively, whereas mean SDV E_{max} for coarsely and finely crushed ORF were lower ($17.25 [$17.93] and $17.01 [$16.39], respectively), and OC placebo was the lowest ($0.37 [$0.60]). Positive controls did not differ significantly from each other ($P \geq .437$) on all three measures.

The pattern of responses for High VAS, Good Effects VAS, and ARCI MBG (data not shown) proved similar for both positive controls; both treatments demonstrated prominent, statistically significant responses versus OC placebo ($P < .001$ for all). ORF scores were intermediate, and OC placebo scores were the lowest.

A post-hoc responder analysis of E_{max}[21] for drug liking of ORF compared to OC found that, among subjects who insufflated both finely crushed ORF and finely crushed OC, a cumulative 57% (n = 16) had some reduction (i.e., >0%) in drug liking, 36% (n = 10) had a reduction of at least 30%, and 29% (n = 8) had a reduction of at least 50% (Figure 2a). A similar analysis comparing ORF to Oxy API found that a cumulative 56% (n = 15) had some reduction in E_{max} of drug liking of finely crushed ORF compared with Oxy API, 33% (n = 9) had a reduction of at least 30%, and 22% (n = 6) had a reduction of 50% (Figure 2b).

Intranasal Tolerability. Overall, scores were low for all treatments on all measures (i.e., the majority of scores were < 1.0), but greater nasal irritation was seen with coarsely and finely crushed ORF. Compared to OC placebo, finely crushed ORF had significantly higher E_{max} on measures of Need to Blow Nose ($P = .017$) and Nasal Congestion ($P = .014$), whereas Oxy API, OC, and
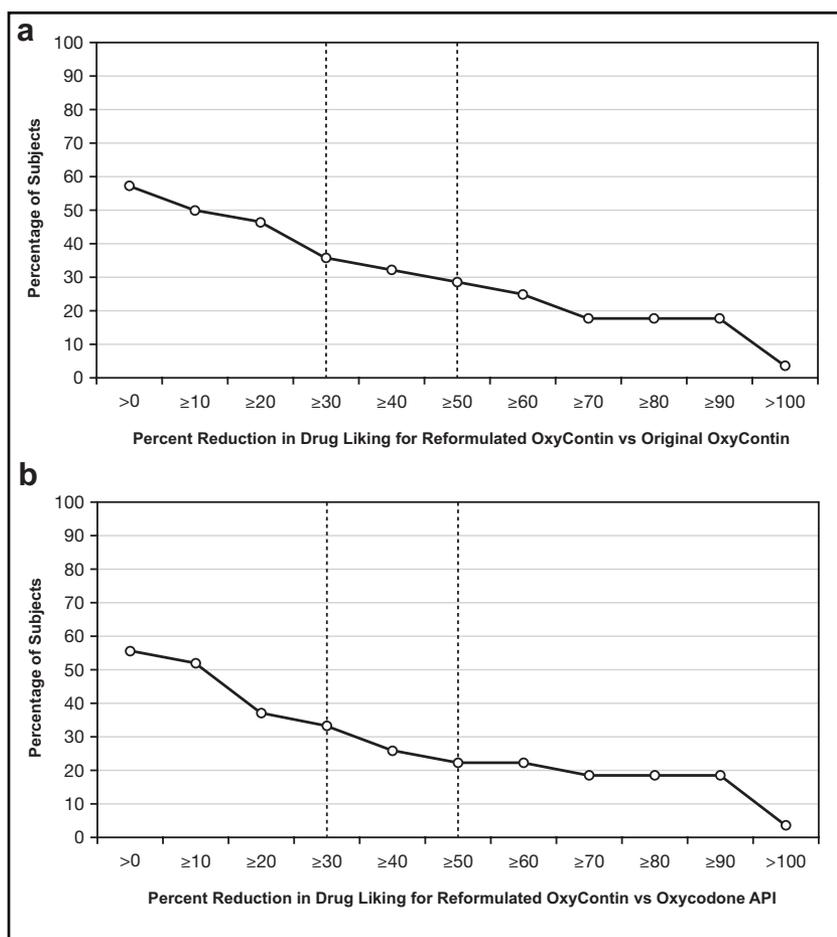

Figure 2. (a) Responder analysis: percent reduction profiles for E_{max} of Drug Liking VAS (finely crushed ORF compared with finely crushed OC). (b) Responder analysis: percent reduction profiles for E_{max} of Drug Liking VAS (finely crushed ORF compared with OXY API).

coarsely crushed ORF did not. Compared to Oxy API, both finely and coarsely crushed ORF had significantly higher E_{max} on both of these measures ($P < 0.01$ for all comparisons). Compared to OC, finely crushed ORF had significantly higher E_{max} on both measures, and coarsely crushed ORF had significantly higher E_{max} for Nasal Congestion only ($P = 0.001$).

Safety

No deaths, severe TEAEs, or other serious AEs occurred. The overall incidence of reported TEAEs, from highest to lowest incidence, was 96.4% for finely crushed OC and 89.7% for Oxy API (positive controls), 86.2% for finely crushed ORF, 75.0% for coarsely crushed ORF, and 41.4% for OC placebo. Most TEAEs were of mild intensity. Only 1 subject experienced a moderately intense TEAE (respiratory depression following finely crushed OC intranasal administration). The most common TEAEs were consistent with the known effects of oxycodone (Table 4). All mean laboratory values and vital signs fell within the normal range at baseline and follow-up, with no notable changes from baseline observed.

Discussion

The abuse-deterrent effects of ORF were evident, in part, in the pharmacokinetic profiles for tampered ORF versus OC, which indicated less potential for abuse of ORF compared with OC based upon a decrease in the rate and extent of oxycodone aborption in the first hours following administration. The pharmacodynamic data collected following ORF demonstrated a reduction in abuse potential compared to OC. These findings provide evidence that the difference in formulation characteristics between OC and ORF observed in in vitro tampering experiments translated

into the intended abuse-deterrent effects on pharmacokinetic and pharmacodynamic properties of ORF.[10] Safety findings proved consistent with the known effects of opioid use and no unexpected safety findings emerged.

Consistent with recent FDA draft guidance,[21] this study of abuse potential was validated by comparing the responses to the positive control treatments with responses to the OC placebo treatment. Intranasal administration of both positive controls, OC and Oxy API, resulted in significant increases in E_{max} for Drug Liking VAS, Overall Drug Liking VAS, and Subjective Drug Value.

The elements of this study are consistent with those recommended in several published guidelines, including: double-blinding; the use of active and OC placebo treatments in a population of nondependent recreational opioid users who were able to discriminate between them via the relevant route of administration; a qualification phase that included a naloxone challenge; the use of opaque vials and particles of crushed treatments that appeared similar across all treatments; primary measures of drug-liking captured on bipolar VAS and expressed in terms of E_{max}; appropriate pharmacokinetic measures (including the rate of the rise of drug concentration); and appropriate additional pharmacodynamic measures (including adequate assessments of intranasal tolerability).[16,21–25] Finally, this study was part of a larger program developed to characterize the abuse potential of ORF.

The comprehensive analysis of the abuse potential of ORF includes a battery of in vitro tamper-testing studies as well as in vivo pharmacokinetic and abuse potential studies.[10,26,27] It also includes a suite of real-world epidemiological studies that compare rates of misuse, abuse, and diversion over the 2-year period since the introduction of ORF with a 15-month pre-introduction baseline period of OC rates.[28] Recently reported results

Table 4. TEAEs Reported by ≥5% of Subjects for Any Treatment at Onset by MedDRA Preferred Term (Safety Population)

TEAEs	Placebo (n = 29)	ORF-F (n = 29)	ORF-C (n = 28)	OC (n = 28)	Oxy API (n = 29)
Any TEAE	12 (41.4)	25 (86.2)	21 (75.0)	27 (96.4)	26 (98.7)
Dizziness	2 (6.9)	1 (3.4)	1 (3.6)	3 (10.7)	3 (10.3)
Dry mouth	0	0	1 (3.6)	1 (3.6)	2 (6.9)
Epistaxis	1 (3.4)	0	1 (3.6)	2 (7.1)	1 (3.4)
Euphoric mood	1 (3.4)	17 (58.6)	12 (42.9)	23 (82.1)	24 (82.8)
Fatigue	0	2 (6.9)	0	1 (3.6)	0
Feeling hot	0	1 (3.4)	1 (3.6)	2 (7.1)	3 (10.3)
Feeling of relaxation	1 (3.4)	1 (3.4)	1 (3.6)	2 (7.1)	1 (3.4)
Headache	0	2 (6.9)	3 (10.7)	1 (3.6)	0
Nasal congestion	2 (6.9)	9 (31.0)	5 (17.9)	2 (7.1)	1 (3.4)
Nausea	1 (3.4)	0	0	3 (10.7)	1 (3.4)
Pruritus	0	6 (20.7)	4 (14.3)	4 (14.3)	8 (27.6)
Pruritus generalized	0	2 (6.9)	0	7 (25.0)	6 (20.7)
Somnolence	3 (10.3)	11 (37.9)	7 (25.0)	9 (32.1)	9 (31.0)
Vomiting	1 (3.4)	0	0	1 (3.6)	2 (6.9)

MedDRA, *Medical Dictionary for Regulatory Activities*, version 9.1; OC, finely crushed original OC; ORF-C, coarsely crushed ORF; ORF-F, finely crushed ORF; Oxy API, oxycodone powder; TEAEs, treatment-emergent adverse events.

from these multiple, ongoing epidemiologic studies support the findings presented here. The epidemiologic study results available to date have shown reductions in overall and tamper-related abuse of OxyContin since the introduction of the reformulation of OxyContin (ORF) in 2010,[29–31] as well as in its street price,[32] and diversion.[33]

In common with limitations of all abuse potential studies,[34] the results of this study do not provide information relating the introduction of this abuse-deterrent formulation to changes in real-world abuse. Another limitation is that current recommendations suggest that cognitive and psychomotor measures be included in opioid abuse potential studies, although it is acknowledged that specific tests have not yet been identified for recommendation.[35] An additional limitation is that, despite measures taken to reduce the opportunity for subjects to make physical comparisons among the study treatments (e.g., treatments were held in opaque vials with preinserted tubes for insufflation), it was not possible to fully prevent such comparisons being made, which may have compromised blinding to some extent. Finally, the outcome measures of this study are acknowledged to be measures of relative abuse potential and not absolute measurements. While the methods themselves appear to have validity, they do not take into account the social context in which ORF appears, including cultural norms and legal strictures on availability. Therefore, the results of this study should be interpreted in proper context: a study that compares an abuse-deterrent reformulation of a product with a product that was previously subject to significant misuse and abuse.

Conclusions

Reformulated OxyContin (ORF) has physicochemical properties intended to deter tampering for the purposes of intranasal oxycodone abuse by making crushing both more difficult and less effective, resulting in a reduction in the rate and extent of oxycodone absorption in the first hours after administration. The pharmacokinetic and pharmacodynamic effects of ORF were seen in this study of healthy adults who were nonphysically dependent, recreational opioid users. Intranasal administration of crushed ORF was associated with reduced C_{max}, increased T_{max}, and lower abuse quotient scores compared with Oxy API and crushed OC. Compared with both original OxyContin (OC) and Oxy API, peak effects of finely and coarsely crushed ORF were significantly lower on most subjective and objective measures (including Overall Drug Liking VAS, Take Drug Again VAS, High VAS, Subjective Drug Value, and pupillometry), and these peak effects occurred later compared with the positive controls. Significant increases in these subjective and objective measures for OC and Oxy API compared to OC placebo confirmed the validity of the study design. ORF exhibited a safety profile consistent with intranasal opioid use in this population. The reduced intranasal oxycodone abuse potential of ORF indicated by the findings of the present study are consistent with the findings of reductions in intranasal oxycodone abuse reported in epidemiologic studies of reformulated OxyContin.[28–33]

Declaration of Conflicting Interests

All authors affiliated with Purdue Pharma L.P. are full-time employees. Dr. Smith was the primary investigator for this study. Dr. Shram and Ms. Bartlett were involved in data interpretation and preparation of the clinical study report. Dr. Sellers was an investigator for this study and is a consultant for Purdue Pharma L.P. Dr. Shram was an employee of INC Research Toronto at the time this study was conducted.

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