Dose-Proportionality, Relative Bioavailability, and Effects of Food on Bioavailability of an Immediate-Release Oxycodone HCl Tablet Designed to Discourage Tampering

Almasa Bass,[a] Kenneth Sommerville,[a] Robert Rolleri,[a] Glenn Pixton,[a] Jeffrey Stark,[b] Cynthia Zamora,[c] Mark Leibowitz[c]; *[a]Pfizer Inc, Cary, NC, USA; [b]Worldwide Clinical Trials Drug Development Solutions, Austin, TX, USA; [c]Worldwide Clinical Trials Drug Development Solutions, San Antonio, TX, USA*

INTRODUCTION

- Prescription drug abuse is a large and growing public health issue.
  - Over 10% of the US population have used prescription pain relievers nonmedically at some point in their lifetime.[1]
- Immediate-release (IR) opioids account for a vast majority of outpatient opioid prescriptions and have a higher proportion of misuse, abuse, and diversion than extended-release formulations.[2,3]
- Nonmedical users of opioids often begin consuming excessive numbers of intact tablets and may progress to chewing or crushing and then ingesting, snorting, or injecting to enhance the onset of euphoria.[4,5]
- An immediate-release oxycodone hydrochloride tablet (IRO-A; **Oxecta™**) was developed using a technology designed to discourage intranasal and intravenous abuse.[6]
- IRO-A was previously shown to be bioequivalent to IR oxycodone tablets (IRO; Roxicodone®) in fasted state (study AP-ADD-100).

OBJECTIVES

- The primary objective of the present study was to determine the dose proportionality of oxycodone in IRO-A tablets under fasted conditions.
- Secondary objectives were to assess the possible effects of food on the pharmacokinetics (PK) of oxycodone in IRO-A tablets, to compare the relative bioavailability of oxycodone in IRO-A tablets relative to that in commercially available IRO tablets under fed conditions, and to evaluate the single-dose safety of the IRO-A tablets in healthy volunteers pretreated with naltrexone.

METHODS

Study Population

- Potential study participants from the greater San Antonio, Texas area were screened and consented.

Main Inclusion/Exclusion Criteria

- Men and women were aged 18 to 55 years and in generally good health, with a body weight of ≥50 kg and a body mass index of 18 to 32 kg/m^2 (inclusive).
- Participants with a history or current evidence of alcohol or drug abuse, those positive for hepatitis B or C virus or human immunodeficiency virus, and those with a history of clinically significant disease or a current medical condition that would jeopardize their safety were excluded.

Study Design

- An open-label, single-dose, randomized, 5-way crossover study with each dose separated by a washout period of ≥7 days.
- Participants were randomized to 1 of 10 treatment sequences using a Williams square design, with a single treatment given per dosing period.
- All participants fasted overnight and were treated with one of the following: IRO-A 1 × 5 mg, IRO-A 2 × 5 mg, and IRO-A 2 × 7.5 mg under fasted conditions, and IRO-A 2 × 7.5 mg and IRO 1 × 15 mg following a high-fat, high-calorie breakfast served 30 minutes before dosing and consumed within 30 minutes.
- Naltrexone HCl 50 mg was administered twice: ~12 hours and 1 hour before study treatment to minimize potential adverse events associated with opioid administration.
- Participants were discharged from the clinical research unit after collection of the 24-hour post-dose blood sample, and then returned to the unit after a washout period of ≥7 days for the next dosing period.

Pharmacokinetic Assessments

- Venous blood samples were drawn at specified times pre- and post-dose on an inpatient basis on study days 1 and 2 during each dosing period.
- Plasma oxycodone levels were measured using a validated assay.
- Oxycodone concentrations below the limit of quantification were treated as 0 from time 0 until the time at which the first quantifiable concentration was observed.
- Calculated PK parameters included maximum plasma concentration (C_{max}), time to C_{max} (T_{max}), terminal half-life ($t_{1/2}$), area under the concentration–time curve from time 0 to the time of the last quantifiable concentration (AUC_{last}), and area under the plasma concentration–time curve from time 0 extrapolated to infinity (AUC_{inf}).

Safety Assessments

- Adverse events, vital signs, and pulse oximetry were recorded during each dosing period.
- Electrocardiogram and clinical labs were recorded during screening and end of study.

Statistical Analyses

- All participants who received at least 1 dose of study drug were included in the safety population.
- The PK population was defined as all participants who had at least 1 PK blood sample taken following administration of study drug.
- The oxycodone plasma concentration–time data were analyzed by noncompartmental methods using WinNonlin® software, version 4.0 (Pharsight Corporation, Cary, NC, USA).
- Dose proportionality of oxycodone was assessed using 3 approaches: (1) confidence interval (CI), (2) linear regression, and (3) power model.
- For the CI approach and the linear regression analysis, the C_{max}, AUC_{last}, and AUC_{inf} values for individual participants were normalized to the 5-mg dose.
- Food effect and relative bioavailability were assessed with the CI approach.
- Safety parameters were analyzed descriptively.

RESULTS

Patients

- Thirty-five participants were enrolled in this study, 28 completed all 5 dosing periods, 33 completed at least 1 dosing period, and 7 discontinued (reasons: vomiting, n=4; protocol noncompliance, n=2; and withdrew consent, n=1).
- Participant demographic characteristics are shown in **Table 1**.

Table 1. Participant Demographics

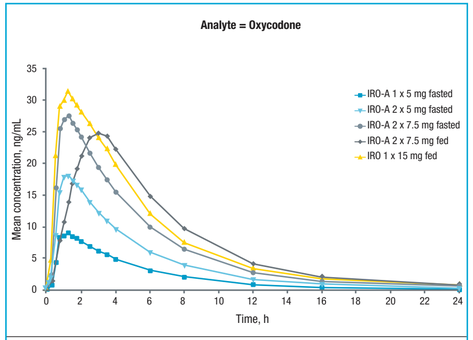
Characteristic	Summary statistics
Age, y	
Mean ± SD	32.6 ± 11.1
Range	18–55
Sex, n (%)	
Male	19 (54)
Female	16 (46)
Race, n (%)	
White	24 (69)
Black or African American	9 (26)
Asian	1 (3)
American Indian or Alaska Native	1 (3)
Ethnicity, n (%)	
Hispanic or Latino	17 (49)
Not Hispanic or Latino	18 (51)
Weight, kg	
Mean ± SD	75.5 ± 12.3
Range	56.2–98.1
Body mass index, kg/m^2	
Mean ± SD	25.7 ± 3.07
Range	18.7–30.6

SD, standard deviation.

Pharmacokinetics

- For all treatments, oxycodone was quantifiable by 15 minutes and C_{max} was reached in a median of 1.25 hours after administration of the IRO-A tablets in the fasted state (**Figure 1, Table 2**).
- Oxycodone exposure (C_{max}, AUC_{last}) increased in proportion to dose following administration of the 5-mg, 10-mg, and 15-mg IRO-A tablets in the fasted state (**Figure 1, Table 2**).

Figure 1. Mean Oxycodone Plasma Concentration–Time Profiles



IRO-A, immediate-release oxycodone hydrochloride tablet; IRO, immediate-release oxycodone.

Table 2. Pharmacokinetic Parameters of Oxycodone by Treatment

	IRO-A 5 mg (fasted)	IRO-A 10 mg (fasted)	IRO-A 15 mg (fasted)	IRO-A 15 mg (fed)	IRO 15 mg (fed)
Participants, n	31	30	30	29[a]	30
T_{max}, h					
Median	1.25	1.25	1.25	3.00	1.00
Range	0.75–3.50	0.50–2.03	0.50–3.00	1.25–6.00	0.50–4.00
C_{max}, ng/mL					
Mean ± SD	10.0 ± 3.08	19.9 ± 5.64	32.9 ± 9.09	28.5 ± 7.37	37.7 ± 11.30
CV%	30.8	28.3	27.6	25.9	29.9
AUC_{last}, h•ng/mL					
Mean ± SD	45.38 ± 12.65	93.19 ± 25.46	152.9 ± 41.11	178.8 ± 44.58	186.3 ± 50.13
CV%	27.9	27.3	26.9	24.9	26.9
AUC_{inf}, h•ng/mL					
Mean ± SD	47.40 ± 13.07	95.50 ± 25.64	155.4 ± 41.57	184.1 ± 45.02	189.2 ± 51.23
CV%	27.6	26.9	26.8	24.5	27.1
$t_{1/2}$, h					
Mean ± SD	3.24 ± 0.61	3.38 ± 0.60	3.57 ± 0.58	3.71 ± 0.55	3.74 ± 0.59
CV%	18.9	17.7	16.3	14.8	15.9

IRO-A, immediate-release oxycodone hydrochloride tablet; IRO, immediate-release oxycodone; T_{max}, time to maximum drug concentration; C_{max}, maximum plasma concentration; SD, standard deviation; CV, coefficient of variation; AUC_{last}, area under the plasma concentration–time curve from time 0 to the time of the last quantifiable concentration; AUC_{inf}, area under the plasma concentration–time curve extrapolated to infinity; $t_{1/2}$, terminal elimination half-life.

[a] n=28 for assessments of AUC_{inf} and $t_{1/2}$.

- When analyzed using the CI approach, the 90% CIs calculated for the geometric mean ratios of dose-normalized C_{max}, AUC_{last}, and AUC_{inf} for IRO-A 10 mg versus 5 mg and for IRO-A 15 mg versus 5 mg were all within the limits of 80% to 125% (**Table 3**).
- Comparable results were obtained in the linear regression analysis of dose-normalized C_{max}, AUC_{last}, and AUC_{inf}.
  - The 95% CIs bracketed 0 and the slopes were not significant (C_{max}: 95% CI, –0.0551 to 0.2475, P=0.2098; AUC_{last}: 95% CI, –0.1027 to 1.2183, P=0.0968; AUC_{inf}: 95% CI, –0.2334 to 1.1109, P=0.1980).
- Results from the power model are presented in **Table 4**.
- The power model showed proportionality across the 3 dependent variables tested.

Table 3. Statistical Analysis of Dose Proportionality of the Dose-Normalized, Natural Logarithm–Transformed Pharmacokinetic Exposure Parameters of Oxycodone in the Fasted State Using the CI Approach

Parameter[a]	Geometric mean[b]		Ratio, %	90% CI	Power	ANOVA CV%
	IRO-A 10 mg	IRO-A 5 mg	10 mg/5 mg			
C_{max}, ng/mL	10.1263	10.2645	98.65	92.74–104.95	0.9999	13.02
AUC_{last}, h•ng/mL	47.8522	47.0572	101.69	96.80–106.83	1.0000	10.36
AUC_{inf}, h•ng/mL	49.0234	49.0616	99.92	95.10–104.99	1.0000	10.41
	IRO-A 15 mg	IRO-A 5 mg	15 mg/5 mg			
C_{max}, ng/mL	10.9429	10.0949	108.40	101.49–115.78	0.9998	14.42
AUC_{last}, h•ng/mL	50.5041	45.5402	110.90	105.47–116.61	1.0000	10.97
AUC_{inf}, h•ng/mL	51.3901	47.5657	108.04	102.77–113.58	1.0000	10.92

IRO-A, immediate-release oxycodone hydrochloride tablet; CI, confidence interval; ANOVA, analysis of variance; CV, coefficient of variation; C_{max}, maximum plasma concentration; AUC_{last}, area under the plasma concentration–time curve from time 0 to the time of the last quantifiable concentration; AUC_{inf}, area under the plasma concentration–time curve extrapolated to infinity.

[a] PK parameters for IRO-A 10 mg and 15 mg were dose normalized to the 5-mg dose by dividing the parameter values by 2 and 3, respectively.

[b] The geometric mean was determined from the least squares mean of the logarithm-transformed values.

Table 4. Assessment of Dose Proportionality for Oxycodone Following Administration of IRO-A Tablets in the Fasted State Using a Mixed-Effects Statistical Model Based on a Power Function[a]

Dependent variable	Model variable	Estimate (β_1)	*P* value	90% CI	Dose P[b]
C_{max}	ln(Dose)	1.0698	<0.0001	1.0140–1.1256	9.8746
AUC_{last}	ln(Dose)	1.0887	<0.0001	1.0426–1.1348	8.4530
AUC_{inf}	ln(Dose)	1.0645	<0.0001	1.0188–1.1102	13.5932

IRO-A, immediate-release oxycodone hydrochloride tablet; CI, confidence interval; C_{max}, maximum plasma concentration; AUC_{last}, area under the plasma concentration–time curve from time 0 to the time of the last quantifiable concentration; AUC_{inf}, area under the plasma concentration–time curve extrapolated to infinity.

[a] Power model: $\ln(PK\ variable) = \ln(\beta_0) + \beta_1 \times \ln(Dose) + \varepsilon$, where $\ln(\beta_0)$ is the y-intercept, β_1 is the slope, and ε is the error term.

[b] Highest dose ratio for which dose proportionality would be demonstrated.

- Administration of IRO-A 15 mg following intake of a standard, high-calorie, high-fat breakfast resulted in ~14% reduction in the oxycodone C_{max} and a ~21% increase in the oxycodone AUC_{last} and AUC_{inf} compared with the same dose of IRO-A in the fasted state (**Table 5**).
- The 90% CIs for the geometric mean ratios for C_{max}, AUC_{last}, and AUC_{inf} were not within the accepted limits of 80% to 125% for bioequivalence, which suggest the presence of a food interaction with IRO-A during oxycodone absorption (**Table 5**).
- Food caused a delay in T_{max} from 1.25 hours to 3.00 hours after administration of IRO-A 15 mg compared with the fasted state (**Figure 1, Table 2**).

Table 5. Statistical Analysis of Natural Logarithm–Transformed Pharmacokinetic Exposure Parameters of Oxycodone Following Administration of IRO-A 15 mg in the Fed and Fasted States

Parameter	Geometric mean[a]		Ratio, %	90% CI	Power	ANOVA CV%
	Fed	Fasted	Fed/Fasted			
C_{max}, ng/mL	28.7442	33.3062	86.30	79.34–93.88	0.9952	16.71
AUC_{last}, h•ng/mL	181.1176	149.6582	121.02	113.41–129.14	0.9998	12.86
AUC_{inf}, h•ng/mL	184.3175	151.9725	121.28	113.72–129.35	0.9998	12.75

IRO-A, immediate-release oxycodone hydrochloride tablet; CI, confidence interval; ANOVA, analysis of variance; CV, coefficient of variation; C_{max}, maximum plasma concentration; AUC_{last}, area under the plasma concentration–time curve from time 0 to the time of the last quantifiable concentration; AUC_{inf}, area under the plasma concentration–time curve extrapolated to infinity.

[a] The geometric mean was determined from the least squares mean of the logarithm-transformed values.

- When administered under fed conditions, IRO-A 15 mg had bioavailability comparable to IRO based on the analysis of AUC_{last} and AUC_{inf} (**Table 6**).
- IRO-A administration resulted in a decrease of ~16.5% in C_{max} compared with IRO, and the geometric mean ratio of C_{max} was not contained within the 80% to 125% range, which indicates that these 2 products are not bioequivalent for C_{max} under fed conditions (**Table 6**).

Table 6. Statistical Analysis of Natural Logarithm–Transformed Pharmacokinetic Exposure Parameters of Oxycodone Following Administration of IRO-A 15 mg or IRO 15 mg in the Fed State

Parameter	Geometric mean[a]		Ratio, %	90% CI	Power	ANOVA CV%
	IRO-A	IRO	IRO-A/IRO			
C_{max}, ng/mL	28.5363	34.1786	83.49	76.66–90.93	0.9945	17.21
AUC_{last}, h•ng/mL	174.3790	175.6501	99.28	94.43–104.37	1.0000	10.05
AUC_{inf}, h•ng/mL	177.3905	178.3980	99.44	94.56–104.56	1.0000	10.10

IRO-A, immediate-release oxycodone hydrochloride tablet; IRO, immediate-release oxycodone; CI, confidence interval; ANOVA, analysis of variance; CV, coefficient of variation; C_{max}, maximum plasma concentration; AUC_{last}, area under the plasma concentration–time curve from time 0 to the time of the last quantifiable concentration; AUC_{inf} = area under the plasma concentration–time curve extrapolated to infinity.

[a] The geometric mean was determined from the least squares mean of the logarithm-transformed values.

Safety

- Adverse events following IRO-A and IRO administration were similar (**Table 7**).
- All treatment-emergent adverse events were rated by the investigator as mild to moderate in intensity.
- No serious adverse events occurred during this study.

Table 7. Treatment-Emergent Adverse Events Reported by ≥2 Participants in Any Treatment Group[a]

Adverse event, n (%)	IRO-A 5 mg (fasted) (N=32)	IRO-A 10 mg (fasted) (N=31)	IRO-A 15 mg (fasted) (N=30)	IRO-A 15 mg (fed) (N=31)	IRO 15 mg (fed) (N=31)
Nausea	7 (22)	6 (19)	7 (23)	6 (19)	5 (16)
Headache	2 (6)	2 (6)	4 (13)	6 (19)	4 (13)
Abdominal pain	1 (3)	0	3 (10)	4 (13)	4 (13)
Dizziness	3 (9)	2 (6)	3 (10)	3 (10)	1 (3)
Vomiting	1 (3)	1 (3)	0	2 (6)	1 (3)
Abdominal distention	0	0	1 (3)	3 (10)	0
Dry mouth	0	2 (6)	0	0	1 (3)
Flatulence	0	0	2 (7)	0	1 (3)

[a] Includes adverse events occurring from administration of study treatment until administration of naltrexone in the next dosing period.

CONCLUSIONS

- **The present study showed that IRO-A tablets are dose proportional between 5 mg and 15 mg under fasted conditions.**
- **Administration of IRO-A with food resulted in small changes in oxycodone PK compared with the fasted state. However, these are not expected to be clinically significant; therefore, IRO-A can be taken without regard to food.**
- **AUCs were equivalent, and C_{max} was lower, following IRO-A versus IRO in the fed state.**
- **The single doses of IRO-A were well tolerated.**

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