



The Effect of Different C_{max}/T_{max} Ratios on Euphoria and Liking Following Oral Oxycodone Dosing in Opioid-Experienced, Non-Dependent, Recreational Drug Users

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A subject discontinuation phase consisted of safety procedures performed 24 hours after each subject's last dose.

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Introduction

► Prescription opioid abuse is a serious problem that has attracted much attention in recent years. Particularly alarming are the high rates of non-medical use of prescription pain relievers among adolescents. In 2007, 9.6% of 12th graders reported nonmedical use of Vicodin® hydrocodone/acetaminophen (APAP) and 5.2% reported non-medical use of OxyContin® (oxycodone). Despite the prevalence of oxycodone abuse, there is little information in the public domain regarding its human abuse liability. Of the published studies, none have evaluated a controlled-release formulation of oxycodone and none have reported on the pharmacokinetics (PK) of oxycodone or the relationship between its PK and abuse liability. Based on the limited information available on the abuse liability of oxycodone, further studies (particularly PK-PD) are needed to understand the problem occurring today with prescription opioid abuse. The pharmaceutical industry is developing new formulations intended to be more difficult to manipulate and abuse. The putative benefit of the new formulations is based upon the PK and PD effects, yet there is little data to support the concept that different PKs will influence the abuse potential of a drug. Therefore, this study was designed to explore the relationship between abuse potential (determined by "likeability" and "euphoria") and the PK profile (C_{max} and T_{max}) over a clinically relevant range of doses of oxycodone.

Objective

► The primary objective of the study was to evaluate the relationship between the pharmacokinetics of oral oxycodone and the pharmacodynamic endpoints, which are specific measures of abuse-liability in opioid-experienced, non-dependent, recreational drug users.

Methods

► The randomized, double-blind, placebo-controlled, crossover study contained 2 cohorts of opioid-experienced, non-dependent, recreational drug users. All subjects underwent a naloxone challenge and were screened for the ability to discriminate between 40 mg oxycodone and placebo. Qualifying subjects proceeded to the double-blind abuse-liability phase. Inclusion criteria included 18 to 50 years of age, male with a history of recreationally abusing opioids defined as having experienced a "high" on at least 5 occasions in the last 12 months and once in the past 90 days. Subjects who abused multiple drugs had to prefer opioids. They could not be physically dependent on any drug of abuse and/or alcohol (excluding nicotine), as assessed by the Investigator and DSM-IV criteria.

Methods

Cohort 1 explored the PK-PD relationship of oxycodone formulations. Cohort 2 explored the PK-PD relationship of different oxycodone doses.

► Cohort 1 received 1 treatment per day on 5 consecutive days: 40 mg IR oxycodone (Immediate Release) in a capsule (two 20 mg tablets); 40 mg CR oxycodone (Controlled Release) in a capsule (1 tablet crushed); 40 mg CR oxycodone in a capsule (1 tablet intact); 80 mg CR oxycodone in a capsule (two tablets intact); and placebo capsule.

► Cohort 2 received 1 treatment per day on 4 consecutive days: 20 mg IR oxycodone in a capsule (1 tablet); 40 mg IR oxycodone in a capsule (two 20 mg tablets); 80 mg IR oxycodone in a capsule (four 20 mg tablets); and placebo capsule.

The primary endpoints were the Drug Effects Questionnaire (DEQ) questions, "Do you like the drug?" (DEQ #4) and "How high are you now?" (DEQ #5).

PK endpoints included the T_{max} , C_{max} , and AUC at 0.25, 0.50, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, and 12 hours after dosing, calculated via plasma samples and compared to PD effects.

The relations between DEQ #4 and DEQ #5 scores at T_{max} and C_{max} were assessed. The relation of the abuse quotient (AQ) to the AUE of DEQ #4 and DEQ #5 was assessed for intervals 0-15, 0-30, 0-45, 0-60, 0-90 minutes for each dose. The AQ is C_{max}/T_{max} .

Results

36 subjects were enrolled

18 subjects completed the abuse liability phase in cohort 1. 16 subjects completed the abuse liability phase in cohort 2. No subject withdrew due to AE's or safety issues

Figure 1. Cohort 1 shows that the relation of E_{max} to T_{max} could not be clearly assessed since C_{max} was not held as constant as the study was attempting to perform by the original design; Cohort 2 shows excellent correlation of E_{max} to a change in C_{max} for both DEQ 4 ($R^2 = 0.8448$) and DEQ 5 ($R^2 = 0.9661$).

Figure 2 shows the PK of all doses in Cohort 1 and 2

Figures 3 and 4 show the mean DEQ #4 and DEQ #5 at each PK sample time for both Cohort 1 and 2.

Figure 5 shows excellent correlation of AQ to liking (DEQ #4) from 15 to 60 minutes and very good correlation up to 90 minutes using the AUE of DEQ #4 for each time point.

Figure 6 shows excellent correlation of AQ to euphoria (DEQ #5) up to 60 minutes but a lesser correlation from 0 to 90 minutes using the AUE of DEQ #5 for each time point

**Tmax vs Liking (DEQ #4)
Tmax vs Euphoria (DEQ #5)**

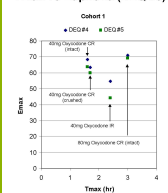
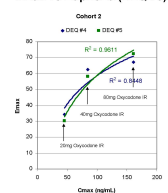


Figure 1

**Cmax vs Liking (DEQ #4)
Cmax vs Euphoria (DEQ #5)**



PK Parameters

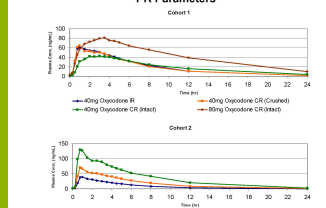


Figure 2

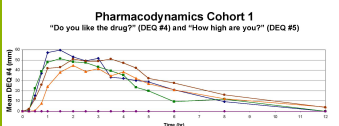


Figure 3

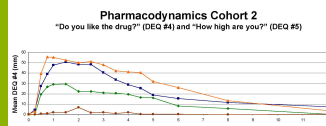


Figure 4

**Abuse Quotient vs Drug Liking
"Do you like the drug?"**

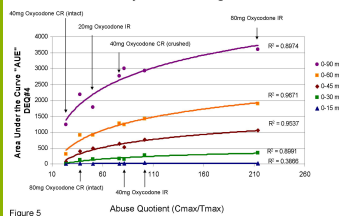


Figure 5

**Abuse Quotient vs Euphoria
"How high are you?"**

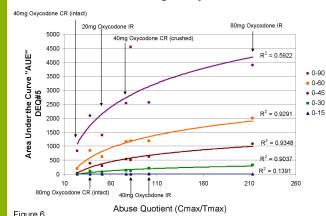


Figure 6

Discussion

This is the first study to show the relationship between oxycodone liking and Euphoria to the pharmacokinetics, T_{max} and C_{max} over a clinically relevant range of doses. Basic science research has suggested that the abuse potential of an opioid is related to its C_{max} and T_{max} but the relative importance of each has not been elucidated. This study suggest C_{max} correlates well with the degree of "likeability" and magnitude of a "high". However we could not determine if a change in T_{max} also correlates with E_{max} since the PK of C_{max} across treatment groups was not controlled. Further exploration of this relationship is required. There was a strong correlation with the ratio of C_{max}/T_{max} which supports the construct that the evaluation of the AQ may be a reasonable assessment for the potential of abuse. This is due to the strong relationship found for the AQ ratio to the likeability of oxycodone (0 to 90 minutes). Likewise, excellent correlation was found for the AQ to euphoria (0 to 60 minutes). Increasing the C_{max} (dose) during the 0-90 minutes did not produce proportional increase in euphoria. This could mean that once you are "high" additional drug can not continue to produce proportional euphoria. The PK data suggest whole CR oxycodone has an immediate release component which may influence the AQ. Although this data does not support direct correlation of T_{max} and E_{max} the AQ data suggest that this may have an influence on abuse potential, the extent of this influence would need to be further explored in future studies.

Conclusion

• A range of 20 to 80 mg IR oxycodone can be safely administered to healthy subjects for research purposes.

• E_{max} for "liking" and "euphoria" strongly correlates with C_{max}

• If liking and euphoria effects drive oxycodone abuse, then an AQ value may help determine the abuse potential of oxycodone formulations. A high AQ value may help identify preferred drugs and formulations sought by recreational prescription drug abusers. Conversely a low AQ value may suggest less attractiveness as a drug of abuse.

• Further research is needed to determine if indeed this construct will hold true over time and with other opioids and classes of compounds at risk for abuse, misuse, and diversion