Pharmacokinetic-Pharmacodynamic (PK/PD) Analyses in the Assessment of Abuse-Deterrent Opioid Formulations (ADFs)

Megan Shram[1], Salvatore Colucci[2], Stephen Harris[2], Peter Perrino[2], Naama Levy-Cooperman[1], Kerri Schoedel[1], Sharon Walsh[3]

[1] Altreos Research Partners, Inc.; [2] Purdue Pharma L.P.; [3] Department of Behavioral Science, University of Kentucky.

Introduction

- The goal of PK/PD analysis is to assist in predicting the effect of a drug over time in relation to exposure
- In terms of abuse, the relationship between rate of rise of drug concentration and effect is considered important (fast onset/short action → increased abuse potential)
- However, multiple factors contribute to the overall drug experience (**Figure 1**)
- Food and Drug Administration (FDA) Draft Guidances on the Assessment of Abuse Potential of Drugs and Abuse-Deterrent Opioids indicate:[1,2]

"*Characterization of the PK/PD properties…is important for determining the abuse potential of a…product.*"

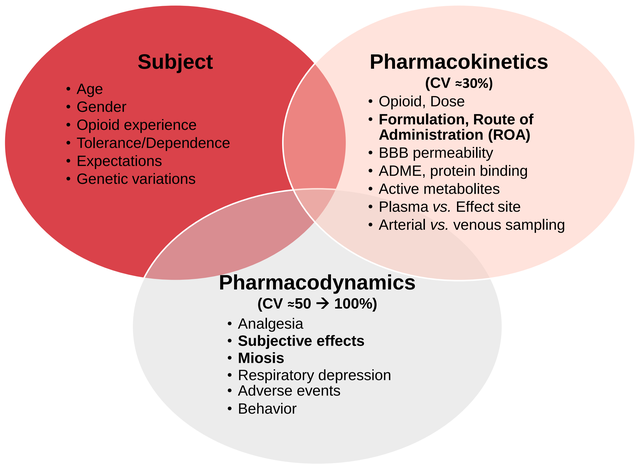
"*PK data should be collected to correlate with the PD outcomes.*"

"*The rate of rise of drug onset for the intact and manipulated potentially ADF should be given appropriate weight in the overall analysis.*"

Aim

To explore the role of PK in abuse deterrence assessment and its relationship to PD in recreational drug users

Figure 1. Potential Sources of Variability



Note: Items in bold are considered in the present analysis
BBB = blood brain barrier; CV= coefficient of variation

Methods

Analyses are based on data previously collected during abuse potential trials in recreational opioid users conducted in Lexington, Kentucky, Columbus, Ohio (Ohio Clinical Trials), and Toronto, Canada (INC Research Toronto, Inc.).

Rate of Rise: Peak concentration/effect (C_{max}/E_{max}), time to peak (T_{max}/TE_{max}) and rate of rise of oxycodone concentrations/Drug Liking visual analog scale [VAS]) scores of oxycodone administered via oral, intranasal (IN) and/or intravenous routes were determined and compared (Kruskal-Wallis/Wilcoxon signed rank tests, 2-sided α= 0.05).

Correlations: Pearson correlations (r) were conducted for subjective (Drug Liking VAS) and objective (pupillometry) responses relative to plasma drug concentration (derived parameters and matched by timepoint) following IN administration of ADFs:

- Physicochemical Barrier: Reformulated OxyContin® 30 mg, crushed fine and coarse (n=29)
- Physicochemical Barrier: Hydrocodone extended-release (HYD) 60 mg, crushed fine and coarse (n=27)
- Agonist/Antagonist: Oxycodone/Naloxone (OXN) 30/15 mg, crushed (n=29)
- Non-ADF reference: Original OxyContin® 30 mg, crushed (n=29)

Results

How does rate of rise relate to Drug Liking?

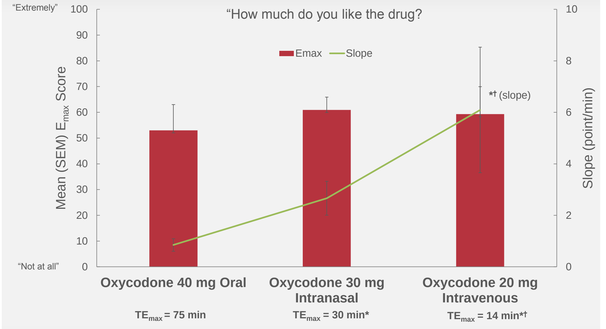
Table 1. Mean (SD) of Derived Parameters and Rate of Rise (Slope) for Oxycodone Plasma Concentration and Drug Liking VAS

N=35	IR Oxycodone Oral, intact 30 mg	IR Oxycodone Intranasal, crushed 30 mg
Pharmacokinetics		
C_{max} (ng/mL)	55.0 (15.5)	50.2 (12.7)
T_{max} (min)[a]	69.5 (18 – 370)	99.0 (18 - 370)
Slope (ng/mL per min)	+1.04 (0.66)	+0.71 (0.52)
Drug Liking VAS		
E_{max}	85.8 (16.7)	90.5 (11.9)
TE_{max} (min)[a]	69.0 (7.8 – 720)	31.0 (7.8 – 244)
Slope (point per min)	+0.78 (0.59)	+1.62 (1.25)*
PK/PD Correlation (Pearson's r)	**+0.57**	**+0.35**

IR=immediate-release; SD = standard deviation.
Data collected within-subject. Drug Liking administered as bipolar 100-point VAS: "At this moment, my liking for this drug is…", where 0=Strong disliking, 50=Neither like nor dislike, 100=Strong liking.
Timepoints up to individual T_{max}/TE_{max} used in slope calculation. PK/PD correlations (by timepoint) up to median T_{max} for each route
*p<0.05. Significantly different from oral route. R values in bold indicate statistically significant correlation (p<0.05). [a]T_{max}/TE_{max} presented as median (range).

How does ROA affect magnitude and timing of Drug Liking?

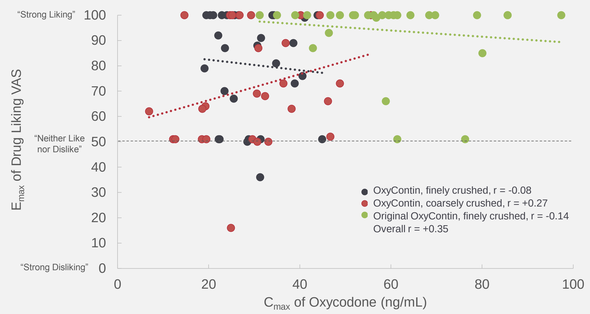
Figure 2. Rate of Rise and Drug Liking of Oxycodone by ROA



SEM= standard error of the mean. Unipolar 100-point VAS. Between subject: oral, n=9; intranasal, n=20; intravenous, n=9.
TE_{max} and Slope: *p<0.05. significantly different from oral route, †p<0.05, significantly different from intranasal route.

Does PK/PD differ as a function of the abuse-deterrent mechanism, measure and/or endpoint?

Figure 3. Scatterplot of E_{max} of Drug Liking VAS and C_{max} of Oxycodone for Intranasally Administered Manipulated OxyContin®[3]



Bipolar 100-point Drug Liking VAS: "At this moment, my liking for this drug is…"

Table 2. Pearson Correlations (r) between Opioid Exposure and Effect following IN Administration of Manipulated Opioid Formulations

Abuse-Deterrent Mechanism	Drug Liking VAS		Pupil Diameter	
	C_{max} vs. E_{max}	Matched by Timepoint	C_{max} vs. MPC	Matched by Timepoint
Non-ADF				
Original OxyContin®, crushed	-0.14	**+0.25**	+0.09	**-0.46**
Physicochemical Barrier				
OxyContin®, finely crushed	-0.08	**+0.23**	**-0.63**	**-0.39**
OxyContin®, coarsely crushed	+0.27	**+0.33**	**-0.40**	**-0.60**
HYD, finely crushed	**+0.37**	**+0.36**	**-0.53**	**-0.46**
HYD, coarsely crushed	**+0.32**	-0.13	**-0.77**	**+0.08**
Agonist/Antagonist				
OXN, crushed (oxycodone/naloxone)	+0.17/+0.11	-0.16/+0.09		

MPC=maximum pupil constriction; Drug Liking VAS administered as a bipolar 100-point scale.
Values in bold indicate statistical significance (p<0.05)

Summary of Results

- Rate of rise in Drug Liking increased with speed of drug delivery, resulting in an earlier TE_{max}; however, E_{max} itself did not significantly differ by ROA (**Table 1, Figure 2**)
- Rate of rise & shorter TE_{max} for Drug Liking could be associated with central exposure not adequately represented by venous plasma PK under certain conditions (**Table 1**)
- PK/PD correlations indicate weaker relationship for IN route *vs.* oral route; however, more frequent PK sampling may be necessary to fully characterize IN PK
- Correlations between C_{max} and Drug Liking E_{max} were generally modest regardless of abuse-deterrent mechanism, although a stronger relationship was observed with physical manipulations resulting in more variable exposure (**Table 2, Figure 3**).
- Matched timepoint analyses generally show stronger, statistically significant relationship *vs.* derived parameters
- Oxycodone exposure was more closely related to physiological response *vs.* subjective Drug Liking

Discussion and Conclusions

- Rate of rise and TE_{max} show marked differences across route of administration, although peak Drug Liking (E_{max}) is not significantly different.
- Because their mechanism is intended to alter opioid exposure when manipulated, ADFs that are more likely to demonstrate a significant PK/PD relationship include:
  - Physicochemical barrier (though may vary with manipulation)
  - Prodrugs
- Since their mechanism is not intended to alter opioid exposure, ADFs that are less likely to demonstrate a PK/PD relationship include:
  - Agonist/antagonist combinations
  - Aversion technology
- **Due to multiple factors contributing to the subjective drug experience, PK alone is not expected to adequately characterize or predict abuse deterrence, and may further depend on the abuse-deterrent mechanism under study.**

References

1. FDA. Draft Guidance for Industry: Assessment of Abuse Potential of Drugs, January 2010.
2. FDA. Draft Guidance for Industry: Abuse-Deterrent Opioids – Evaluation and Labeling, January 2013.
3. Harris SC, Perrino PJ, Smith I, Shram MJ, Colucci SV, Bartlett C, Sellers EM. Abuse potential, pharmacokinetics, pharmacodynamics, and safety of intranasally administered crushed oxycodone HCl abuse-deterrent controlled-release tablets in recreational opioid users. J Clin Pharmacol. 2014;54(4):468-477.

Disclosure: Supported by Altreos Research Partners, Inc. and Purdue Pharma L.P.

Presented at CPDD, San Juan, Puerto Rico, June 14-19, 2014