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

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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 Guidelines on the Assessment of Abuse Potential of Drugs and Abuse-Deterrent Opioids indicate:1,2
  1 Characterization of the PK/PD properties...a important for determining the abuse potential of a product.
  2 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

Pharmacodynamics (CV ~10%)
• Analgesia
• Pharmacokinetic effects
• Misses
• Respiratory depression
• Adverse events
• Behavior

Pharmacokinetics (CV <10%)
• Age
• Gender
• Opioid experience
• Tolerance/Dependence
• Expectations
• Genetic variables

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

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 (V12 Research, Toronto, Inc.).

Rate of Rise: Peak concentration/Effect (Cmax/Emax) time to peak (Tmax/Emax) and rate of rise of oxycodone concentrations/Dog Liking Variate at each timepoint (VAS) scores of oxycodone administered via oral, intranasal (IN) and intravenous routes were determined and compared (Kruskal-Wallis/Wilcoxon signed rank tests; α = 0.05).

Results

How does rate of rise relate to Drug Liking?

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

<table>
<thead>
<tr>
<th>Route</th>
<th>Parameter</th>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral</td>
<td>Cmax (μM)</td>
<td>59.2 (12.7)</td>
</tr>
<tr>
<td></td>
<td>Tmax (min)</td>
<td>69.5 (18.5)</td>
</tr>
<tr>
<td></td>
<td>Slope (μM/min)</td>
<td>+0.25 (0.14)</td>
</tr>
<tr>
<td>IN</td>
<td>Cmax (μM)</td>
<td>50.2 (12.7)</td>
</tr>
<tr>
<td></td>
<td>Tmax (min)</td>
<td>69.5 (18.5)</td>
</tr>
<tr>
<td></td>
<td>Slope (μM/min)</td>
<td>+0.25 (0.14)</td>
</tr>
<tr>
<td>IV</td>
<td>Cmax (μM)</td>
<td>50.2 (12.7)</td>
</tr>
<tr>
<td></td>
<td>Tmax (min)</td>
<td>69.5 (18.5)</td>
</tr>
<tr>
<td></td>
<td>Slope (μM/min)</td>
<td>+0.25 (0.14)</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Correlation</th>
<th>Non-ADF</th>
<th>ADF</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax vs. Emax</td>
<td>-0.46</td>
<td>-0.46</td>
<td>0.04</td>
</tr>
<tr>
<td>Tmax vs. Emax</td>
<td>-0.38</td>
<td>-0.38</td>
<td>0.04</td>
</tr>
<tr>
<td>Slope vs. Emax</td>
<td>-0.51</td>
<td>-0.51</td>
<td>0.04</td>
</tr>
<tr>
<td>Cmax vs. Drug Liking VAS</td>
<td>+0.46</td>
<td>+0.46</td>
<td>0.04</td>
</tr>
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</tr>
</tbody>
</table>

Discussion and Conclusions

• Rate of rise and TEmax show marked differences across route of administration, although peak Drug Liking (EEmax) 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:
  - Pharmacobiological barrier (through may with manipulation)
  - Prodrugs
- Since their mechanism is not intended to alter opioid exposures, 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 experience, PK alone is not expected to adequately characterize or predict abuse deterrents, and may further depend on the abuse-deterrent mechanism under study.

References

1 FDA. Draft Guidance for Industry: Abuse-Deterrent Formulations for Opioids; December 2012.

Notes: Some variables are present in the present analyses.
ADF = Abuse Deterrent Formulation; Na = standard error of the mean; SD = standard deviation; Tmax = time to peak; Emax = maximum effect; Cmax = maximum concentration.