Insights from structural model deliniate PK associated with abuse potential following intranasal administration in recreational drug users

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Objectives: Development of abuse deterrent opioids has been viewed as an important steps towards containing the opioid epidemic. Because opioid products are often manipulated for purposes of abuse, sufficient understanding of the pharmacokinetics (PK) following various routes of administration is required. The objective if this study is to characterize the PK of oxycodone following intranasal (IN) administration.

Methods: Plasma concentration-time data (756 observations) from 42 subjects participating in a abuse potential study was used to develop a population PK (pop-PK) model for oxycodone. One-, two-, and three-compartment models with and without lag-time were tested to characterize the fast absorption of oxycodone after insufflation followed by a second slower absorption phase of swallowed drug product from the gastrointestinal tract. Interindividual differences in the rate and extent of absorption due to differences in the subjects’ ability to insufflate the oxycodone drug product were considered in this non-linear mixed effects modelling (NLME) approach performed in Phoenix, NLME 1.3. The final model was selected based on the goodness of model fit, physiological meaningfulness of parameter estimates, nonparametric bootstraps, and visual predictive checks.

Results: Our final model was able to simulatenously characterize all data reasonably well. The structure of the model incorporated absorption from both IN and oral (stomach) compartments into the systemic circulation. Transit compartments accounted for the delay of oral absorption due to the drug transition from nasal cavity into the stomach. The structural parameter for the fraction of the dose absorbed through oral route vs absorbed through nasal mucosa was included in the model. This parameter accounts for differences in insufflation experiences between the recreational drug users.

A structural and statistical model was developed to describe the PK of insufflated oxycodoneand characterize both IN and oral complex absorption processes. The model demonstrated population variability in the relative amounts of drug absorbed from IN and oral routes which could be a measure of variability in subjects' prior experience and individual demographics.

Figure: Representative oxycodone profiles for the subjects with preferentially fast nasal absorption (blue), slow oral absorption (yellow) and mixed profile (red).

Conclusions: We developed a pop-PK that was able to simulataneously characterize the PK of oxycodone following IN and oral absorption as well as associated variability. The model will now be linked to pharmacodynamic markers to characterize the benefit-risk profile of oxycodone following intended use and abuse.