Identifying Critical Parameters for Physiological Based Pharmacokinetic Modeling of Naloxone Hydrochloride Nasal Sprays

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Purpose

Naloxone hydrochloride (HCl) is a potent opioid antagonist that is used as a rescue drug for opioid overdose and provides a quick onset of action for the reversal of opioid-related respiratory depression. Naloxone HCl was first approved in the U.S. as a nasal spray in 2015, but only two generic products of naloxone HCl nasal spray have been approved. For this study, physiologically based pharmacokinetic (PBPK) modeling is applied to identify the sensitivity of model parameters that may impact pharmacokinetics (PK) metrics such as the maximum plasma concentration (C_{max}), the time to C_{max} (T_{max}), the area-under-the-concentration-time-curve (AUC), the nose fraction absorbed (F_a%), and the fraction bioavailable (F%). Concurrently, an in silico nasal model is being developed to model naloxone HCl in opioid agonist and antagonist combination products with abuse deterrent properties. The results of this study are expected to provide information on which parameters may be used to model intranasal dosing of naloxone. Future naloxone modeling is expected to help determine critical study design parameters when comparing the abuse deterrent properties of opioid agonist and antagonist combination products when administered through nasal insufflation.

Methods

A comprehensive search of available data revealed three clinical PK data sets for naloxone HCl nasal sprays (one new drug application [NDA] and two abbreviated new drug applications [ANDA], all in the 4 mg strength). The naloxone model was developed as a full-body PBPK model and integrated with the pulmonary compartment absorption and transit (PCAT) module using GastroPlus™ (Version 9.8.2. Simulations Plus, Inc., Lancaster, CA, USA) to support intranasal dosing. Physiochemical properties were obtained from the literature or in silico predictions. The parameters in the full-body PBPK model were adjusted to fit volume of distribution and clearance to intravenous and oral naloxone plasma concentration data available in the literature.[1,2] For the PCAT model, the nasal tissue permeability and the percentage of drug unbound in mucus for the nose and extra-thoracic compartments were adjusted to fit the plasma concentration data for a 0.4 mg naloxone HCl nasal spray dose.[3]

Naloxone HCl nasal sprays were modeled as immediate-release formulations. The predictions of the naloxone models were validated against naloxone plasma concentration data from clinical PK studies where naloxone nasal spray was administered as a single 4 mg spray in one nostril. A parameter sensitivity analysis was then conducted for the model.

Results

The naloxone model predictions were compared to mean clinical study data. For the NDA product, the naloxone model predictions resulted in a 3.8% difference in C_{max} and a 7.9-minute difference in T_{max} with a 37.7% difference in AUC. For the ANDA products, the naloxone model predictions resulted in 10.7% and 0.93% difference in C_{max}, 13-minute and 18-minute difference in T_{max} with a 46.5% and 47.8% difference in AUC, respectively.

Sensitivity analyses showed that the parameters in the model with the largest influence on PK metrics were nose percent drug unbound in mucus, extra-thoracic percent drug unbound in mucus, nose permeability, and mucociliary clearance time.

Model predictions showed that C_{max}, AUC, F_a, and F were affected by different nose permeability values ranging from 1.3e-6 to 2.56 cm/s, but T_{max} was not. Additionally, nose percent drug unbound in mucus and extra-thoracic percent drug unbound in mucus were each sensitive over the range of 0.5-100%. The mucociliary clearance time was found to be a sensitive parameter over the range of 0.035-0.5 h with respect to all PK metrics.

Conclusions

PBPK models were developed to predict PK metrics for naloxone HCl nasal spray. The results showed agreement with available in vivo PK data. PK metrics were sensitive to differences in nose permeability, which may be due to the relatively large amount of drug that was predicted to be absorbed intranasally. The parameter sensitivity analysis also demonstrated that nose percent drug unbound in mucus, extra-thoracic percent drug unbound in mucus, and mucociliary clearance time are sensitive parameters. The accuracy of these findings may potentially be explored with future experiments.

The developed naloxone models may serve as useful tools for understanding drug delivery of naloxone in the nasal route. These may provide information in the future on the parameters that may be sensitive to modeling nasal insufflation of opioid combination products with abuse deterrent properties containing naloxone.

References

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