Physiologically Based Pharmacokinetic Modeling of Naloxone Hydrochloride Nasal Sprays

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Disclaimer

- ***This presentation represents the views and perspectives of the speaker and does not necessarily reflect the views of the FDA.***

Objectives

- ***Upon completion, participants will be able to explain the purpose, model structure, and approach for PBPK modeling of nasal drug products, including naloxone nasal spray formulations.***

Nasal Spray Modeling

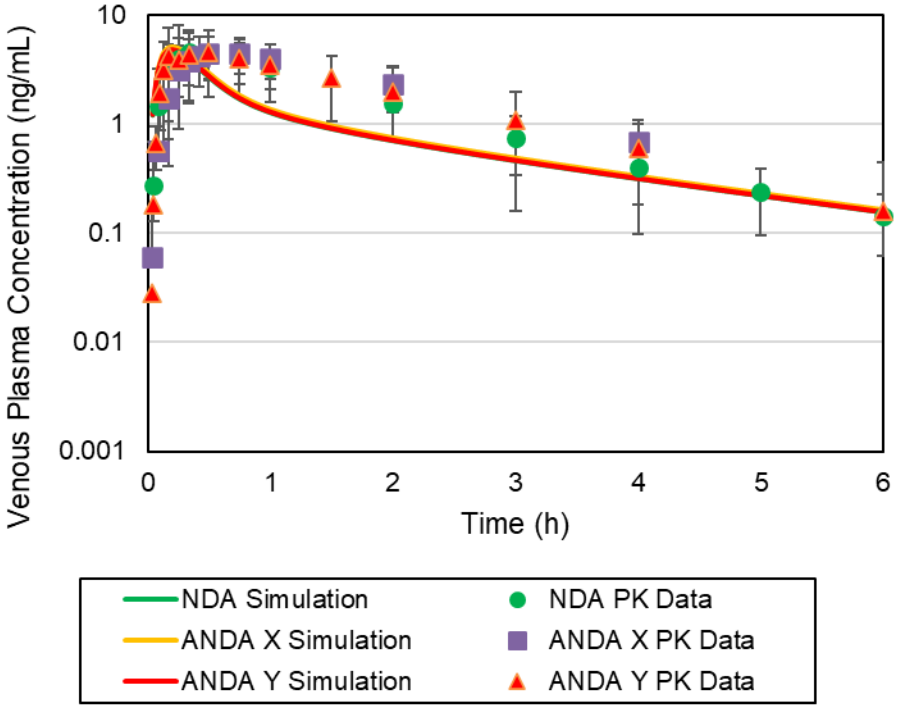
- Currently, two generic products of naloxone hydrochloride (HCl) nasal spray have been approved.
- A physiologically based pharmacokinetic (PBPK) model to simulate the pharmacokinetics (PK) of naloxone HCl nasal spray was constructed using the GastroPlus PCAT (pulmonary compartment absorption and transit) model.
- The PCAT model includes separate compartments for regions of the lungs (extra-thoracic, thoracic, bronchiolar, alveolar-interstitial) and a compartment for the nose.
- The mucociliary clearance mechanism removes drug from the lung compartments and nose to the stomach compartment within the gastrointestinal model (ACAT model) for absorption.

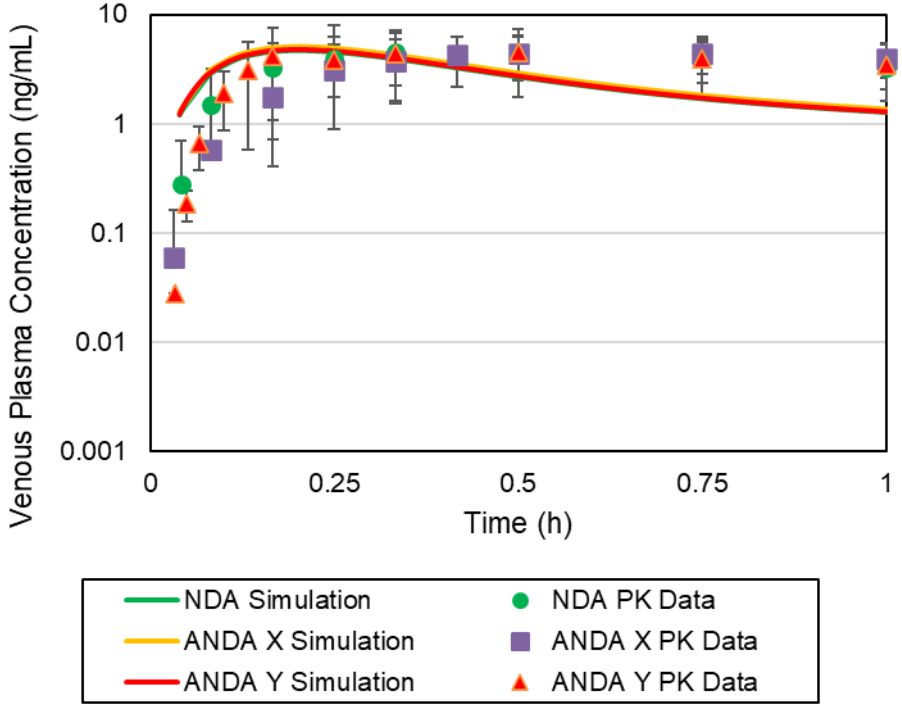
Nasal Spray Modeling

- Nasal Absorption Assumptions:
  - Passive absorption is the dominant absorption process.
  - Metabolism of naloxone does not occur in the nose.
  - Nasal dose is instantaneously dissolved into the nasal mucosa.
- 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.
- PK predictions were validated against naloxone plasma concentration data from clinical PK studies of naloxone HCl nasal spray (4 mg, one nostril).
- A parameter sensitivity analysis was conducted on the PCAT model parameters.

Model Validation

- The PK predictions from the model were validated against naloxone plasma concentration data from naloxone HCl nasal spray clinical PK studies.





Parameter Sensitivity Analysis

- The parameter sensitivity analysis is performed on 11 selected variables in the PCAT model.
- The ranges of parameter values are selected based on minimum and maximum permissible values for each parameter.

Parameter	Range
Nose Percent Drug Unbound in Mucus	0.5 - 100 %
Extra-thoracic Percent Drug Unbound in Mucus	0.5 - 100 %
Nose Systemic Rate Constant	0.00396 - 0.016 s^{-1}
Extra-thoracic Systemic Rate Constant	0.00396 - 0.016 s^{-1}
Nose Permeability	1.3e-6 - 2.56 cm/s
Extra-thoracic Permeability	1.3e-6 - 2.56 cm/s
Diffusion Coefficient	0.1 - 1x10^{-5} cm^2/s
Drug Particle Density	0.12 - 12 g/mL
Mean Drug Particle Radius	2.5 - 500 µm
Pulmonary Solubility	4.20 - 16.82 mg/mL
Mucociliary Clearance Time	0.035 - 0.5 h

Parameter Sensitivity Analysis Results

- Positive correlation is indicated by ↑, inverse correlation is indicated by ↓, and negligible relationship is indicated by -.
- The model sensitivity to nose permeability may be due to the relatively large amount of drug that was predicted to be absorbed intranasally.
- The PK metrics were sensitive to percentage of drug unbound in mucus for both the nose and extra-thoracic compartments.
- The drug particle density, mean drug particle radius, and diffusion coefficient were not sensitive which is to be expected for a nasal spray solution.

Parameter	C_{max} (ng/ml)	T_{max} (h)	AUC_{0-t} (ng-h/ml)	F_a (%)	F (%)
Nose Percent Drug Unbound in Mucus	↑	↑	↑	↓	↑
Extra-thoracic Percent Drug Unbound in Mucus	↑	↑	↑	↓	↑
Nose Systemic Rate Constant	-	-	-	-	-
Extra-thoracic Systemic Rate Constant	-	-	-	-	-
Nose Permeability	↑	-	↑	↑	↑
Extra-thoracic Permeability	-	-	-	-	-
Diffusion Coefficient	-	-	-	-	-
Drug Particle Density	-	-	-	-	-
Mean Drug Particle Radius	-	-	-	-	-
Pulmonary Solubility	-	-	-	-	-
Mucociliary Clearance Time	↑	↓	↑	↓	↑

Cmax: the maximum plasma concentration; Tmax: the time to (Cmax), AUC0-t: the area-under-the concentration time curve between 0 and T; Fa%: the nose fraction absorbed; F%: the fraction bioavailable.

Conclusions and Regulatory Impact

- Conclusions:
  - The naloxone PBPK model identified key process parameters for drug absorption for a naloxone nasal spray.
  - Further research to acquire experimental data is warranted to confirm the findings.
  - The impact of device changes on PK could be explored by coupling a computational fluid dynamics model with the existing PBPK model.
- Regulatory Impact:
  - The developed naloxone model may serve as a useful tool for understanding absorption of naloxone in the intranasal route of administration.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