Physiologically-Based Pharmacokinetic Model to Describe the Pharmacokinetics of Crushed Morphine Sulfate and Naltrexone Hydrochloride Extended-Release Capsules with Abuse Deterrent Properties

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PURPOSE

A combination drug product of an opioid agonist and an opioid antagonist may deter end users from abusing the product if separation of the antagonist component from the agonist component is difficult. However, attempts to manipulate these products may result in a final powder that is characterized by various particle size distributions (PSDs) for each individual drug component. A prior study of oxycodone hydrochloride (HCl) extended-release (ER) tablets, an opioid drug product with abuse deterrence properties, showed that a PSD of 100 to 500 microns compared to a PSD of 500 to 1000 microns for milled oxycodone tablets affected peak plasma concentrations (C_{max}) and time to C_{max} (T_{max}).[1] Morphine sulfate and naltrexone HCl ER capsules contain an opioid agonist component and an opioid antagonist component, which upon physical manipulation, the contents of the capsules are released to deter abuse through intravenous (IV), oral, and nasal routes of administration. As morphine sulfate and naltrexone HCl ER capsule beads may be easily manipulated by crushing to a size range of less than 500 microns, an understanding of the effects of non-narrow and non-specific PSDs below 500 microns on the intranasal absorption of morphine and naltrexone is important. The objective of the research is to apply a physiologically-based pharmacokinetic (PBPK) modeling approach to investigate the influence of PSD on pharmacokinetics (PK) of morphine and naltrexone following intranasal dosing of crushed morphine sulfate and naltrexone HCl formulations. PBPK modeling is used to determine the effects of the crushed product PSD on the intranasal absorption as measured by systemic exposure, such as C_{max}, area-under-the-concentration-time curve (AUC), and T_{max}. This study may provide information on how PSD affects the intranasal absorption of crushed morphine sulfate products characterized by a PSD between 100 and 500 microns.

METHODS

- Morphine sulfate and naltrexone HCl were modeled separately as immediate-release formulations because the ER mechanism does not remain intact following physical manipulation (Figure 1).
- Morphine and naltrexone have independent metabolic pathways and no known PK-based drug interactions between the two drugs.
- Initial simulations were executed in GastroPlus™ (V9.7, Simulations Plus, Inc., Lancaster, CA, USA).
- Observed concentration–time profiles for an IV dose in healthy human subjects obtained from the literature were fitted to a three-compartment PK model. [2,4]
- Physicochemical properties were obtained from *in vitro* measurements or optimized predictions (clearance, intestinal permeability). The liver first-pass extraction of 90% was used for the naltrexone simulations and 80% was used for the morphine simulations.
- Initial modeling of an IV dose and IR oral dose simulations are shown in Figure 1 with validation against literature data.[2,3,4]
- For intranasal dosing, morphine sulfate and naltrexone HCl were modeled using the Pulmonary Compartmental Absorption and Transit (PCAT™) module with the nose compartment added.
- Morphine sulfate was modeled using a 30 mg intranasal powder dose and naltrexone HCl was modeled using a 1.2 mg intranasal powder dose.
- A mean particle size of 50 microns was selected for a fine powder.
- The results of the individual PBPK models were validated against data from a nasal insufflation clinical study of a crushed morphine sulfate and naltrexone HCl ER capsule published in the literature.[5] The models were then used to predict the effect of PSD ranges between 100 and 500 microns on PK parameters.

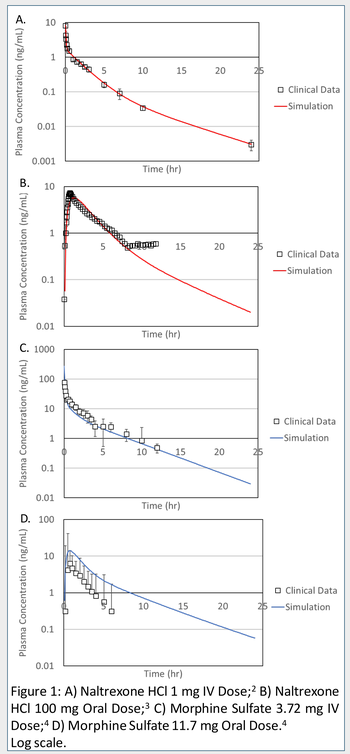

Figure 1: A) Naltrexone HCl 1 mg IV Dose;[2] B) Naltrexone HCl 100 mg Oral Dose;[3] C) Morphine Sulfate 3.72 mg IV Dose;[4] D) Morphine Sulfate 11.7 mg Oral Dose.[4] Log scale.

RESULTS

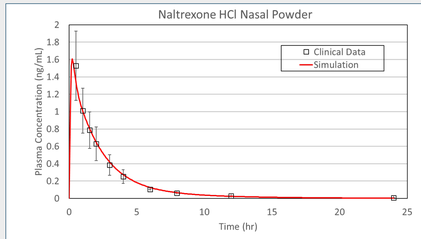

Figure 2A: PK results for naltrexone mean ± SD plasma concentration-time curve following 30 mg of crushed morphine sulfate/naltrexone HCl[5] (n=31) compared to simulation of 1.2 mg naltrexone HCl nasal powder.

- Compared to mean clinical study data,[5] the naltrexone intranasal dose model predictions resulted in a 9.7% difference in C_{max} and an 11 min difference in T_{max} with a 0.08% difference in AUC.
- The simulation and clinical data are in good agreement. The PBPK models can be applied to further studies.

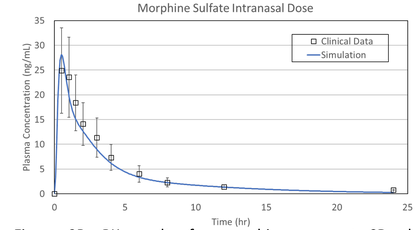

Figure 2B: PK results for morphine mean ± SD plasma concentration-time curve following 30 mg of crushed morphine sulfate/naltrexone HCl[5] (n=31) compared to simulation of 30 mg morphine sulfate nasal powder.

- The morphine intranasal dose model predictions resulted in a 17% difference in C_{max} and no difference in T_{max} with a 0.59% difference in AUC.
- The simulation and clinical data are in good agreement. The PBPK models can be applied to further studies.

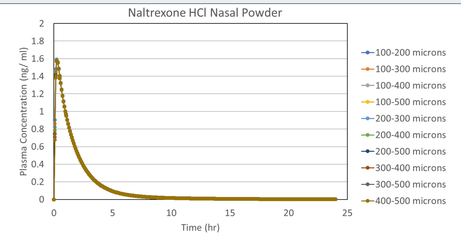

Figure 3A: Plasma concentrations versus time for varying particle size distributions. Naltrexone 1.2 mg dose.

- For naltrexone, the model predicted that plasma concentrations for the PSD ranges were similar for all PSD ranges.
- C_{max}, T_{max}, and AUC were not greatly impacted by the PSD ranges.

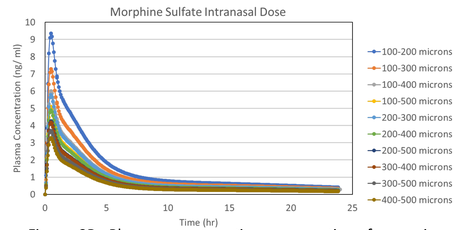

Figure 3B: Plasma concentrations versus time for varying particle size distributions. Morphine 30 mg dose.

- Model predictions showed that C_{max} and AUC of the morphine systemic concentration were affected by different PSDs ranging from 100 to 500 µm.

Table 1: Predicted PK parameter values for morphine and naltrexone following nasal insufflation of crushed morphine sulfate and naltrexone HCl ER capsules, all in the 30 mg/1.2 mg strength, with variable PSD.

- For morphine, there was a 96% difference between C_{max} and a 93% difference between AUC with no change in T_{max} when comparing PSDs in the ranges of 100-200 microns and 400-500 microns.
- For naltrexone, there was a 1.7% difference between C_{max} and a 1.3% difference between AUC with no change in T_{max} when comparing PSDs in the ranges of 100-200 microns and 400-500 µm.

	Morphine			Naltrexone		
	100-200 microns	400-500 microns	100-500 microns	100-200 microns	400-500 microns	100-500 microns
C_{max} (ng/mL)	9.34	3.28	5.09	1.59	1.57	1.58
T_{max} (h)	0.48	0.47	0.47	0.24	0.24	0.24
AUC (ng-h/mL)	35.54	12.97	19.86	2.95	2.92	2.93

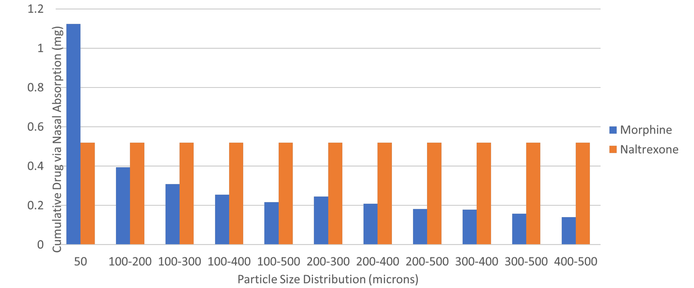

Figure 4: Nasal absorption versus particle size distribution plot for a 30 mg morphine and 1.2 mg naltrexone powder prepared for nasal administration.

- Nasal absorption for both drugs with varying PSDs of 100-500 microns were compared.
- It was found that 0.51 mg (42.5%) of the naltrexone dose and 0.39 mg (1.3%) of the morphine dose were absorbed through the nasal mucosa.
- The remaining drug substance is expected to be absorbed via the oral route through deposition of particles in the stomach by mucociliary clearance[6].

CONCLUSIONS

PBPK models were developed to predict the absorption of crushed morphine sulfate and naltrexone HCl ER beads administered intranasally as a fine powder. The initial results using a fixed particle size of 50 µm showed close agreement with available in vivo data. Model predictions with PSD ranges between 100 and 500 µm showed that morphine systemic concentrations were affected by different PSDs ranging from 100 to 500 µm. On the other hand, PK was independent of the PSD for naltrexone. Particle size differences between the agonist and antagonist could impact the availability of agonist/antagonist ratio which may impact abuse deterrence. The developed models may serve as useful tools for future PBPK studies of opioid formulations.

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