Application of Open-Source PBPK Models in Rat-to-Human Pharmacokinetic Extrapolation of Oral Nicotine Exposures

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Highlights

What?
Application of QSAR and in vivo rat data to predict human PK

How?
Generalized open-source PBPK models; nicotine data

Result
Species scaling and QSAR-derived parameters informed PBPK across routes of interest

Introduction

- Animal data are often used to predict human effects, but dose-response differences in physiology and exposure must be taken into account
- Physiologically based pharmacokinetic (PBPK) models facilitate the tracking of a chemical throughout the body and can be used for inter-species kinetic extrapolation
- This case study utilizes an open-source PBPK model to simulate nicotine after oral/buccal exposures in humans based on in vivo rat oral data and in silico (QSAR) values

Conclusions

- Animal data can assist in optimization of PBPK models to inform PK predictions for human-relevant exposures
- Species-specific exposure routes of buccal and intestinal absorption can have a large impact (>4-fold) when extrapolating from animal data to humans
- High quality in silico QSAR predictions can be useful when in vivo data are limited

References

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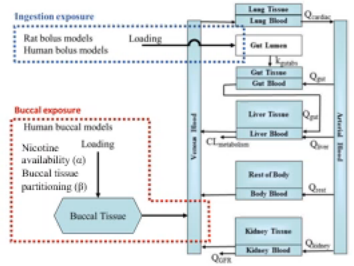
Methods & results

Approach

- Species and exposure routes considered
  - Rat → Oral gavage (gut absorption)
  - Human → Oral gavage (gut absorption)
  - Human → Buccal tissue absorption
- Generalized open-source PBPK models used (Fig. 1, httk v 2.0.2)[1]

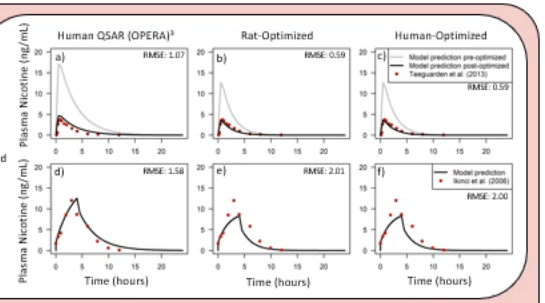
Fig 1: Structure of httk PBPK models . Exposure routes shown by dotted boxes. Figure modified from Wambaugh et al. (2020)[2]



- Default rat PBPK parameterizations (httk[2]) were optimized to fit in vivo rat data
- Rat-optimized parameters were adjusted using allometric scaling to parameterize human gut absorption models
- An adaptation of gut absorption models was used for buccal absorption (Fig. 1)
- Human models parameterized with QSAR predictions[3] or in vivo rat data were compared and validated against independent data sets[5,7]

Human buccal

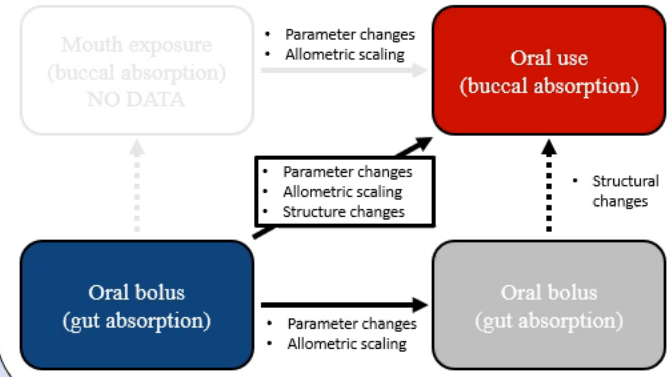
Fig 4:
- *Predicted human plasma profiles following doses of 2 mg[6] (a,b,c) and 6.4 mg[7] (d,e,f) nicotine over 0.5 and 4 hours, respectively.*
- *The buccal adaptation bypassed first-pass metabolism; gut absorption was not included*
- *Buccal absorption parameters optimized to human nicotine gum data[6]*
- *QSAR[3] and in vivo-optimized models preformed similarly*



- Human QSAR- and bolus-based parameters overpredicted data by >4-fold prior to adjustment of buccal absorption parameters using gum data[6]
- Improved performance of QSAR-based[3] buccal model over bolus model suggests the uptake route (gut vs. buccal absorption) was a key factor
- Findings highlight the impact of exposure route on incorporation of animal data into human predictions
- Similar performance of rat- and QSAR-based parameterizations suggests quality QSAR models can be useful when in vivo data are limited

Rat

Human



Rat oral bolus

- Nicotine plasma concentrations from rat gavage (oral bolus) data were collected after 7-day dosing (Test materials: 18% nicotine formulation; up to 8 mg/kg/day)
- Default httk rat parameterization, which is informed by in silico QSAR predictions from OPERA[3], overestimated the in vivo rat data (Fig. 2a)
- Default parameters were optimization by adjusting intrinsic clearance and gut absorption produced a model with an improved fit to the data (Fig. 2b)

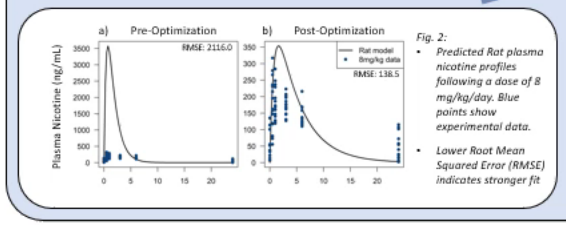


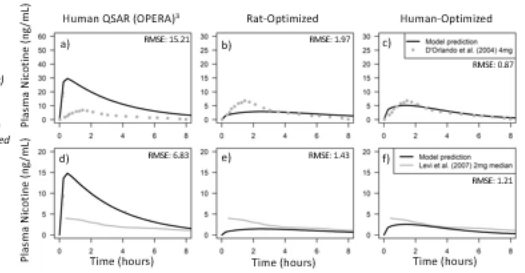
Fig. 2:
- *Predicted Rat plasma nicotine profiles following a dose of 8 mg/kg/day. Blue points show experimental data.*
- *Lower Root Mean Squared Error (RMSE) indicates stronger fit*

- Parameters from the post-optimization were scaled to human physiology and used for human oral bolus prediction in the "rat-optimized" model

Human oral bolus

- Application of rat-optimized parameters to the human model through allometric scaling improved fit for human oral bolus data[4] (Fig. 3a,b)
- Optimization to human bolus data[4] instead of rat data resulted in only minor changes to parameter values and predicted results (Fig. 3c)
- Model predictions optimized to human bolus data[4] fit independent data[5] (Fig. 3d,e,f)

Fig 3:
- *Predicted human plasma nicotine profiles following single doses of 4 mg (a,b,c) and 2 mg (d,e,f) nicotine.*
- *Human-Optimized column shows predictions optimized to the D'Orlando et al. (2004) data[4].*
- *Bottom row shows validation against independent data set.*



The authors declare no conflicts of interest