Physiologically Based Pharmacokinetic Model to Characterize Nicotine Kinetics Following the Use of Oral or Inhalable Products

AUTHORS

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ABSTRACT

Physiologically based pharmacokinetic (PBPK) modeling can be a useful tool for characterizing nicotine pharmacokinetics from use of tobacco products. We expand a previously published PBPK model (Teeguarden et al 2013) to simulate nicotine PK, following single or multiple use of various tobacco products (cigarette, smokeless tobacco and electronic cigarette) and nicotine inhaler (Nicotrol®). The airway section of the model was redesigned to describe 3 uptake compartments: buccal cavity (BC), upper respiratory tract (conducting airways, URT) and lower respiratory tract (transitional airways and alveolar region, LRT). Within each region, the model includes product-specific descriptions of the flux of nicotine into plasma, as well as the flux of nicotine from the BC and URT to the GI tract. These descriptions are based on regional deposition and permeation models of nicotine into plasma. Regional deposition flux combined with regional differences in physiological parameters (eg blood perfusion ratio), play a key role in the product-specific PK profile of nicotine. The current model describes the slower flux of nicotine into plasma across the BC and URT, as well as the rapid flux known to occur in the alveolar region. Overall, the addition of the BC and respiratory tract compartments to the nicotine model provided simulation results that are comparable to the nicotine time-course plasma concentrations reported from clinical studies. The model predictions of mean nicotine plasma levels at specific time points (using the average amount of product used in the clinical study, as model inputs), showed good fits with mean nicotine levels measured from clinical studies (average of individual PK curves). The R^2 values between the model prediction and actual clinical plasma levels for cigarette, electronic cigarette and smokeless tobacco were 0.998, 0.959 and 0.997, respectively. This PBPK model may be utilized to understand the likely mechanisms for the differences observed within and across different product types. Such models may also be useful to simulate nicotine PK profiles under different product use behavior scenarios.

INTRODUCTION

- Teeguarden et al (2013) calibrated a PBPK model to rat and human time-course kinetic studies. To simplify the calibration process, the focus was on IV and oral exposure with cigarette use and nicotine gum simulated as direct uptake into plasma.
- Teeguarden model has been expanded to include a BC and respiratory tract using mucous and epithelial tissue layer mass transfer descriptions from the hybrid CFD-PBPK models (Corley et al 2015, Campbell et al 2014, Teeguarden et al 2008).
- In this case, the airway section of the model describes 3 uptake compartments: BC, URT and LRT. Within each region, the model includes product-specific descriptions of the flux of nicotine into plasma, as well as the flux of nicotine from the BC and URT to the GI tract.
- While these models have primarily been used to derive regional gas dosimetry ratios for human health risk assessment, they provide the necessary physiological descriptions to estimate the regional uptake of nicotine.
- The overarching goal is to develop a PBPK model that will allow simulation of nicotine exposure and pharmacokinetics over a wide range of products and use patterns that can serve as a framework for modeling additional ingredients and combustion by-products.

METHODS

PBPK model parameterization

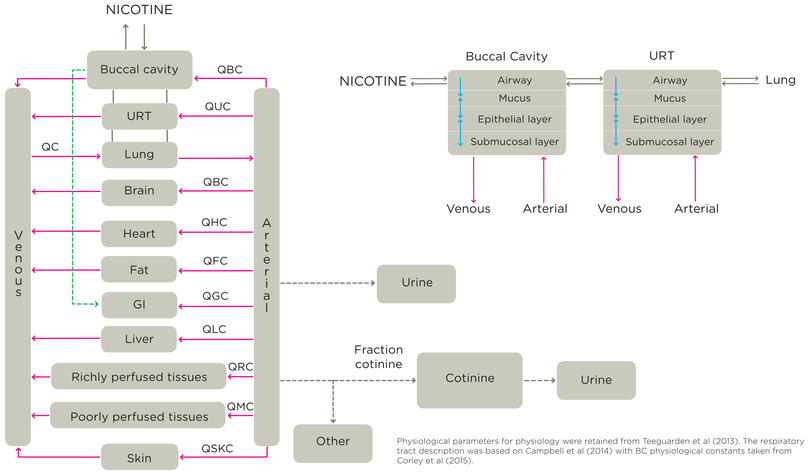
- Teeguarden et al (2013) nicotine PBPK model is used as basis for nicotine distribution and metabolism with ADME parameters unchanged from the reported mean posterior values
- URT consists of 2 sequential compartments representing conducting and transitional airways (Campbell et al 2014)
- BC description taken from Corley et al (2015)
- Exposure routes for nicotine containing products were expanded from simple uptake descriptions to account for bidirectional diffusion of nicotine across the tissue layers (Figure 1 inset)
- Mucous diffusion in URT based on water diffusivity
- Epithelial layer diffusion in URT estimated to provide the best fit to the permeation model expected flux of nicotine and the plasma time-course across all product types
- Diffusion constants were scaled to tissue width and surface area
- Nicotine reaching the lung is assumed to be gas exchange (ie immediate absorption to plasma)
- Simulations conducted using R package DeSolve with MCSim model code

Exposure model

- Human exposure to nicotine from 4 product types (cigarette, E-vapor, MST and Nicotrol® inhaler) used for model development and validation
- Fractional deposition of the inhaled mass of nicotine derived from CFD model (data not shown) for cigarette, E-vapor and inhaler
- Studies simulated were chosen based on the available product use information – puff volume, length, interval and number
- E-vapor and inhaler required estimation of rate nicotine swallowed from BC
- MST use required estimation of the rate of nicotine release from product to mucous along with the rate swallowed and spat to account for the concentration gradient in mucous necessary to generate the plasma time-course

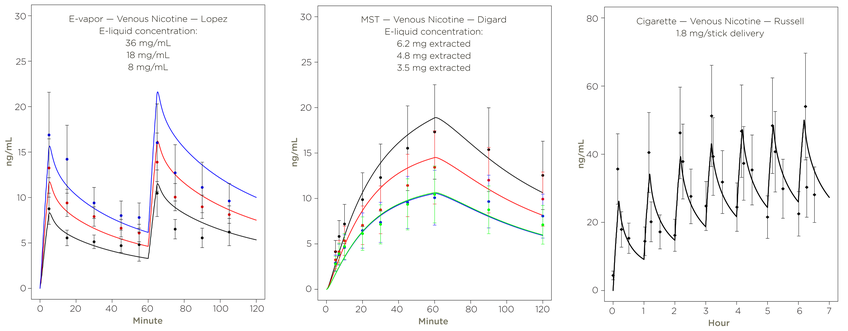
RESULTS

Figure 1. Nicotine PBPK model schematic, including submodel structure for BC and URT (inset).



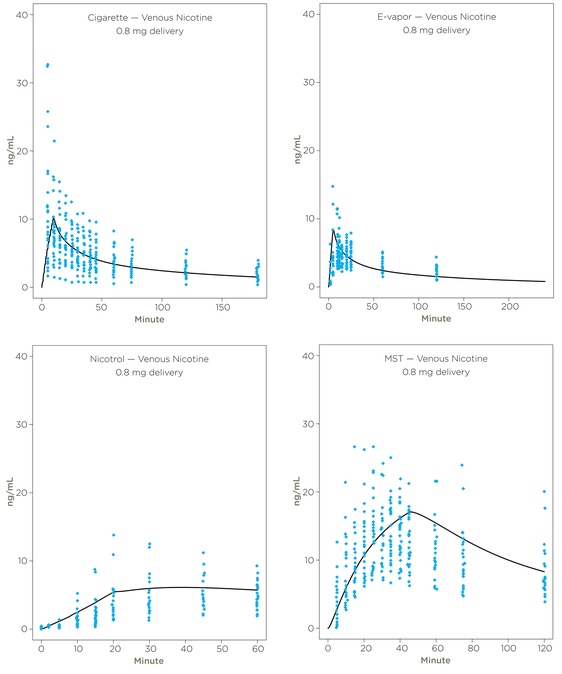
Physiological parameters for physiology were retained from Teeguarden et al (2013). The respiratory tract description was based on Campbell et al (2014) with BC physiological constants taken from Corley et al (2015).

Figure 3. Simulation of 3 published studies nicotine plasma time-course data collected during and after single use of E-vapor (below left, Lopez et al 2015) or MST (below center, Digard et al 2013) or repeated use of conventional cigarette (below right, Russell et al 1976).



For E-vapor and cigarette the intake exposure was estimated to provide the best fit to the time-course data using information provided in the studies. The reported mass released from MST was used to define the exposure to nicotine to simulate Digard et al (2013). For all studies no SD was reported. The figure SD values were based on the CV reported for the AUC to provide visual guidance as to the overall variability in plasma kinetics across subjects and model fit.

Figure 2. Simulation of the venous plasma concentration of nicotine during and after a single use of 1 of the 4 major product types used to estimate the tissue uptake diffusion constant.



Data represent the individual measured concentrations at each time-point. The product types are ordered by their increasing shift to URT and then buccal exposure. The difference between inhaler and MST is higher fraction of mass deposited in BC expected to be swallowed with saliva. The nicotine PBPK model provides a very good agreement to the overall venous plasma time-course data for all product types.

CONCLUSIONS

- The nicotine PBPK model provides simulation results that are comparable to the nicotine time-course plasma concentrations reported from clinical studies across a range of product types
- Model predictions of mean nicotine plasma levels at specific time points (using the average amount of product used in the clinical study, as model inputs), showed good fits with mean nicotine levels
- Where the model deviates from the reported plasma time-course data points to limitations in our exposure paradigm that need to be explored in future studies include product use patterns both within a single use, as well as across repeated uses
- The nicotine PBPK model will be utilized to understand the likely mechanisms for the differences observed within and across different product types and across use events
- The nicotine model provides a platform that will be useful to simulate other constituents delivered with product use

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