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A multi-route model of nicotine–cotinine pharmacokinetics, pharmacodynamics and brain nicotinic acetylcholine receptor binding in humans

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ABSTRACT

The pharmacokinetics of nicotine, the pharmacologically active alkaloid in tobacco responsible for addiction, are well characterized in humans. We developed a physiologically based pharmacokinetic/pharmacodynamic model of nicotine pharmacokinetics, brain dosimetry and brain nicotinic acetylcholine receptor (nAChRs) occupancy. A Bayesian framework was applied to optimize model parameters against multiple human data sets. The resulting model was consistent with both calibration and test data sets, but in general underestimated variability. A pharmacodynamic model relating nicotine levels to increases in heart rate as a proxy for the pharmacological effects of nicotine accurately described the nicotine related changes in heart rate and the development and decay of tolerance to nicotine. The PBPK model was utilized to quantitatively capture the combined impact of variation in physiological and metabolic parameters, nicotine availability and smoking compensation on the change in number of cigarettes smoked and toxicant exposure in a population of 10,000 people presented with a reduced toxicant (50%), reduced nicotine (50%) cigarette Across the population, toxicant exposure is reduced in some but not all smokers. Reductions are not in proportion to reductions in toxicant yields, largely due to partial compensation in response to reduced nicotine yields. This framework can be used as a key element of a dosimetry-driven risk assessment strategy for cigarette smoke constituents.

1. Introduction

The recommendation to establish upper limits for known toxic chemicals in tobacco products (WHO, 2003) is one of many elements of the overarching World Health Organization (WHO) mission to reduce the substantial global burden of disease and death caused by tobacco use (Burns et al., 2008). Recently, the WHO Study Group on Tobacco Product Regulation (TobReg) proposed a strategy for establishing regulatory standards for levels of main stream smoke toxicants involving selection of compounds based on their hazard potential (ranking) and fixing levels relative to nicotine content in cigarettes (Burns et al., 2008). Benchmarking standards for toxicant levels in cigarette smoke relative to nicotine content is intended to prevent inadvertent increases in toxicant exposure driven by changes in smoking behavior induced by changes in cigarette design, nicotine content or nicotine bioavailability. However, a recognizable limitation of both the ranking scheme for chemical toxicants and the benchmarking to nicotine yield is the reliance on external exposure or administered dose.

While exposure based ranking/benchmarking will be an important starting point for assessing and potentially controlling

Abbreviations: AUC, area under the curve; BW, body weight; C_{ant50}, tolerance "concentration"; CLKC, nicotine renal clearance; CLMC, nicotine metabolic clearance; COTCL, total cotinine clearance (unscaled); COTCLC, total cotinine clearance (scaled); CVVB, blood nicotine concentration; FA, fractional availability of nicotine in gum; FNC, fraction of nicotine to cotinine; i.v., intravenous; HRO, basal heart rate; KA, oral uptake rate constant; K_{ant}, first-order rate of loss of tolerance; MCMC, Markov Chain Monte Carlo; MLE, mouth level exposure; nAChRs, nicotinic acetylcholine receptors; PB, brain:blood PC; PBPD, physiologically based pharmacodynamic; PBPK, physiologically based pharmacokinetic; PC, partition coefficient; PD, pharmacodynamic; PM, muscle:blood PC; PR, richly perfused:blood PC; QBC, fractional blood flow to brain; QCC, cardiac output; QMC, fractional blood flow to muscle; QRC, fractional blood flow to richly perfused tissue; QSC, fractional blood flow slowly perfused tissue; S, concentration effect relationship; SC, sensitivity coefficient; TobReg, WHO Study Group on Tobacco Product Regulation; VDC, cotinine volume of distribution; VEIN, nicotine venous concentration; VFC, volume fraction of fat; VMC, volume fraction of muscle; VSLOWC, volume fraction of slowly perfused tissues; VVBC, volume fraction of venous blood; WHO, World Health Organization; L/h/kg$^{0.75}$, liters per hour per kilogram of body weight raised to the three quarters power.

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toxicant levels, a more accurate approach would rank toxicants by internal measures of dose at the site of action (e.g. lung tissue) and standardize toxicant levels to measures of biologically active nicotine levels—nicotine blood levels or nicotinic acetylcholine receptor (nAChR) occupancy levels—rather than mouth level exposure (MLE) or cigarette nicotine levels. Limiting toxicant exposures to biologically active doses of nicotine has several distinct advantages; (a) the greater proximity to the site of biological action reduces confounders, strengthens dose–response relationships and improves the accuracy of hazard rankings; (b) the impact of variability in smoking behavior and inter-individual and population variability on internal doses can be evaluated. Target tissue dosimetry is the preferred measure of dose for chemical risk assessment.

Physiologically based pharmacokinetic (PBPK) and pharmacodynamic (PBPD) models have been used extensively to describe the pharmacokinetics of drugs and environmental chemicals, and their interactions with receptor systems, in some cases for purposes of regulation (Clewell et al., 1997; Clewell and Andersen, 2004; Clewell and Clewell, 2008; Teeguarden et al., 2005a,b; Timchalk et al., 2002). The more recent utilization of PBPK models for evaluating the impact of human variability on internal dosimetry (Bois, 1999; Bois et al., 2010b; Marino et al., 2006; Nong et al., 2008; Yang et al., 2010) is of particular value for understanding nicotine pharmacokinetics; variability in metabolic and physiological parameters has been shown to contribute significantly to variability in drug and chemical dosimetry in blood and tissues (Bucher et al., 2011; Jack, 1985; Regardh, 1985; Routledge, 1985; Welling and Tse, 1984).

PBPK models for nicotine have been developed as an aid to quantify nicotine dosimetry in important tissues compartments, for example, the central nervous system (brain), where key pharmacological effects of nicotine are initiated (Plowchalk et al., 1992; Robinson et al., 1992; Yamazaki et al., 2010). These initial models established a general nicotine–cotinine model framework suitable for extension to explore the influence of human variability in physiological, metabolic and renal clearance parameters, as well as smoking behavior, on nicotine dosimetry, but this opportunity has not been exploited. A focus on only i.v. route pharmacokinetics and calibration using average values for physiological and clearance parameters limit the deployment of the published human models for assessing population level variability and inhalation or oral route pharmacokinetics. The availability of inhalation and oral route human pharmacokinetic data as well as population level statistical characterization of hepatic and renal nicotine and cotinine clearance present the opportunity to extend the exiting human model (Robinson et al., 1992) to better reflect the broader population characteristics of nicotine pharmacokinetics (Benowitz et al., 2002).

Nicotine receptor binding and the pharmacodynamic effects of nicotine are key events in the sequence leading to biological effects. Our evolving understanding of the relationship between blood nicotine concentrations, brain receptor binding and the pharmacodynamic affects have received minimal attention as aspects of internal dosimetry, though preliminary unpublished work has been conducted by Yang and Anderson (Yang et al., 1996).

The objective of this study was to develop, calibrate and test a PBPK model which describes the pharmacokinetics of nicotine and cotinine in humans following i.v., inhalation, and oral exposures. Application of a Bayesian approach for calibration of model parameters from experimental data and prior estimates permitted calculation of the distribution of model parameters, which reflect expected variability in humans. A quantitative description of nicotinic receptor binding in the brain and a pharmacodynamic component describing nicotine effects on heart rate was introduced for the purpose of supporting an alternative basis for establishing limits for cigarette smoke toxicants based on biologically active levels of nicotine. The purpose of the model is twofold: an immediately deployable tool to assure that nicotine dosimetry can be used in a regulatory context to evaluate exposure to, and if necessary, prevent increased exposure to cigarette toxicants as products are reformulated and, longer term, a flexible, biologically-based pharmacokinetic/pharmacodynamic framework that evolves with our understanding of nicotine-receptor interactions and how they contribute to smoking behaviors and nicotine effects.

2. Methods

2.1. Overview of modeling approach

The human nicotine–cotinine PBPK/PD model is a revision and extension of rat and human models developed by Plowchalk et al., 1992 and Robinson et al., 1992, respectively. In order to utilize the extensive clinical literature characterizing nicotine clearance from blood in humans as priors for parameter optimization, nicotine metabolic and renal clearance were applied to the central compartment equivalent, arterial blood. The physiological components of the human model were described according to compartment volumes, ventilation rates and blood flows reported in the literature. Tissue partitioning of nicotine was separated from tissue receptor binding. Tissue receptor binding constants were obtained from the published literature. Revised tissue:blood partition coefficients were developed for the rat model and applied to the human model. The effect of nicotine exposure on cardiac output was captured in a pharmacodynamic model linking blood nicotine concentration to heart rate assuming a constant stroke volume for each individual based on body weight adjusted cardiac outputs. An oral route of exposure was added to simulate blood nicotine pharmacokinetics during the use of nicotine containing gum. Time series sensitivity analyses were conducted to identify parameters with large influences on blood nicotine concentrations which then became targets for optimization. Rate constants for renal clearance and hepatic metabolic clearance of nicotine, the rate constant for nicotine absorption from gum, the fraction of nicotine in gum available for absorption, and the total clearance and volume of distribution of cotinine were optimized against multiple human nicotine blood concentration time course data sets by Markov Chain Monte Carlo (MCMC). MCMC was also used to optimize parameters of the pharmacodynamic model. Total rather than enzyme specific pathways of cotinine and nicotine were considered because it was only necessary to calculate the kinetics of these two materials, not flux through any specific pathway. Renal elimination of cotinine was not tracked because the model was not intended for use in biomonitoring. The resulting model was used to demonstrate how variability in physiological and pharmacokinetic parameters, absolute availability of nicotine in cigarettes, and compensation behavior may affect the smoking behavior and nicotine/toxicant exposure in a population presented with a cigarette with reduced toxicant load and reduced nicotine. All model parameters and their sources are provided in Table 1. The model was coded in acslX (AEgis Technologies Group, Huntsville, AL), is available by request from the authors and can be found in the Supplemental materials.

2.2. PBPK model compartmental structure

The human nicotine PBPK model is similar in structure (Supplemental Fig. 2) to previously published rat and human models (Plowchalk et al., 1992; Robinson et al., 1992). Nicotine and cotinine pharmacokinetics are represented by separate but linked sub-models. Flow-limited (well-mixed) compartments representing the lung, muscle, heart, brain, skin, fat, and richly and slowly perfused tissues (remainder of tissue volume) comprise the