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The acute effects of daily nicotine intake on heart rate – A toxicokinetic and toxicodynamic modelling study

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ABSTRACT

Joint physiologically-based toxicokinetic and toxicodynamic (PBTK/TD) modelling was applied to simulate concentration–time profiles of nicotine, a well-known stimulant, in the human body following single and repeated dosing. Both kinetic and dynamic models were first calibrated by using *in vivo* literature data for the Caucasian population. The models were then used to estimate the blood and liver concentrations of nicotine in terms of the Area Under Curve (AUC) and the peak concentration (C_{max}) for selected exposure scenarios based on inhalation (cigarette smoking), oral intake (nicotine lozenges) and dermal absorption (nicotine patches). The model simulations indicated that whereas frequent cigarette smoking gives rise to high AUC and C_{max} in blood, the use of nicotine-rich dermal patches leads to high AUC and C_{max} in the liver. Venous blood concentrations were used to estimate one of the most common acute effects, mean heart rate, both at rest and during exercise. These estimations showed that cigarette smoking causes a high peak heart rate, whereas dermal absorption causes a high mean heart rate over 48 h. This study illustrates the potential of using PBTK/TD modelling in the safety assessment of nicotine-containing products.

1. Introduction

Nicotine, a commonly used stimulant, has been investigated extensively in previous years, both in terms of *in vivo* and *in vitro* effects on human body. This psychoactive substance is known to increase heart rate, affect the nervous system and influence other biological processes including behavioural effects and metabolic responses (Fattinger et al., 1997; Perkins, 1992). Nicotine is an addictive drug and its consistent use is likely to result in the development of tolerance to (and dependence on) its actions. Cigarette smoking, as a delivery mechanism, is inherently more likely to produce addiction due to the extremely rapid pulmonary absorption of nicotine, occurring at a rate similar to intravenous administration (de Landoni, 1991). There is therefore interest in the development of nicotine replacement therapies based on alternative exposure routes (e.g., coated tablets, chewing gum, nasal spray, inhalator, microtablets and transdermal patches). Cigarettes vary in their nicotine content: the tobacco from bidi cigarettes has on average 21.2 mg/g of nicotine compared to the tobacco from filtered and unfiltered commercial cigarettes containing 16.3 and 13.5 mg/g of nicotine, respectively (Malson et al., 2001). To estimate a daily nicotine consumption, Benowitz et al. (1982) reported that low-, and high- nicotine commercial cigarettes deliver (with Federal Trade Commission [FTC] smoking machine) 1.2, 0.4 and 2.5 mg of nicotine, respectively. Transdermal patches, on the other hand, normally deliver from 5 to 30 mg nicotine and are applied

Abbreviations: A_{org}, C_{org}, amount and concentration of a chemical in given organ/blood [mg], [mg/L]; PC_{org}, organ-to-blood partition coefficients; $f_{\_card}$, cardiac output [L/h]; f_{org}, blood flow rate through organ [L/h]; V_{org}, volume of organ/blood [L]; CLR, renal clearance [L/h]; *fra*, *frb*, *frc*, absorbed fractions that reach liver from stomach, small and large intestine; ka_{stm}, absorption rate from stomach; ka_{SI}, absorption rate from small intestine [L/h]; ka_{LI}, absorption rate from large intestine [L/h]; kel_{LI}, elimination rate from large intestine [L/h]; k_{max}, k_{min}, stomach emptying rates to small intestine; Diss, dissolution rate from a coated tablet [L/h]; D_{SC}, D_{VE}, diffusion coefficients in *stratum corneum* and viable epidermis [cm^2/h]; *k*, release of a chemical from a patch; PC_{SC}, *stratum corneum*/vehicle partition coefficient; PC_{SCVE}, *stratum corneum*/viable epidermis partition coefficient; L_{SC}, L_{VE}, *L*, thickness of *stratum corneum*, viable epidermis, skin [cm]; Area, area of exposed skin [cm^2]; RR, respiratory rate [1/h]; ALV, alveolar ventilation [L/h]; VAT, mucous layer of inhaled/exhaled air [L].

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over 24 h (de Landoni, 1991). *In vivo* experiments showed that less than 100% of the nicotine absolute dose in a patch reaches systemic circulation. The amount of nicotine absorbed has been reported to be between 65% and 90% of the total dose (Bannon et al., 1989; Gupta et al., 1993). This absorption was found independent of a dose and the undelivered amount is believed to be lost either by evaporation or possible skin metabolism.

Papathanasiou et al. (2013) recently studied the effect of nicotine smoking on heart rate at rest and during exercise in 298 young adults. The authors concluded that smokers had significantly higher resting heart rate values than non-smokers but the reverse was observed during exercise. The maximal values achieved during exercise were around 191–193 [bpm] (smokers) and 198–199 [bpm] (non-smokers).

There are many literature studies and reviews describing in detail the absorption, distribution, metabolism and excretion (ADME) processes of nicotine (Benowitz, 1990; Hukkanen et al., 2005).

Nicotine is a water and lipid soluble drug which, in the free base form, is readily absorbed via respiratory tissues, skin, and the gastrointestinal (GI) tract. Plasma protein binding was reported to be only around 5% (Yamazaki and Kanaoka, 2004). Nicotine readily reaches organs and tissues and undergoes extensive metabolism mainly in the liver by cytochrome P450 enzymes (mostly CYP2A6, and also by CYP2B6). A major metabolite of nicotine is cotinine (ca. 80% of nicotine conversion). Other metabolites include nicotine *N′*-oxide, nornicotine, nicotine isomethonium ion, 2-hydroxynicotine and nicotine glucuronide. Renal clearance accounts for up to 35% of total nicotine clearance (Tutka et al., 2005). Additionally, there are observed differences in plasma concentrations between smokers and nonsmokers suggesting differences in total clearance rates, with non-smokers showing faster clearance than smokers (Tutka et al., 2005; Yun et al., 2008). The apparent volume of distribution of nicotine was determined in one clinical study to be 2.0 L/kg in smokers and 3.0 L/kg in nonsmokers (Ellenhorn, 1988).

Due to rich literature resources and experimental data availability nicotine is a good candidate for further elaboration of joint Physiologically-based Toxicokinetic/Pharmacokinetic (PBTK/PBPK) and Toxicodynamic/Pharmacodynamic (PBTD/PBPD) models. Moreover, nicotine has a rapid onset of action therefore it can be used to model observable acute effects. Toxicodynamics is however a highly complex process and sensitive to the development of a physiological tolerance with respect to stimulant dose–response relationships. The theoretical framework should consequently be able to account for such "force-driving" tolerance and thereby reduce the effect of the drug (for instance, via incorporation of a "tolerance" compartment representing a hypothetical noncompetitive antagonist receptor, as described below). Various PBTK–TD models for nicotine are reported in the literature (Green et al., 1999; Porchet et al., 1988; Robinson et al., 1992; Teeguarden et al., 2013) and all present relatively simple but nevertheless satisfactory representations of the nicotine ADME process following the inhalation, dermal, and oral exposure routes.

The aim of this study was to apply a refined PBTK model (with the addition of sub-compartments in skin and GI tract and modification for drug effects) with respect to models previously developed in the scientific literature to simulate selected daily exposure scenarios of nicotine (both in terms of cigarette smoking and nicotine replacement therapy). The internal blood and liver concentrations are defined by the Area Under Curve (AUC) and the peak concentration (C_{max}) and are linked to the TD model which estimates one of the common acute effects, heart rate (mean and its trend in time), both at rest and during cycling exercise. This study builds on previous work by further applying PBTK/TD modelling to analyse nicotine ADME profiles resulting from various exposure conditions based on both single and repeated dosing.

2. Materials and methods

2.1. Experimental data used to calibrate and validate the PBTK model

For the purpose of this study we used the most complete *in vivo* dataset we could find in the public literature for the Caucasian population. For calibration of liver metabolism rates of nicotine to cotinine intravenous experimental data were used (Porchet et al., 1988). In this study, eight healthy subjects (all habitual smokers), in a state of rest, were given two intravenous (i.v.) administrations of nicotine (2.5 μg of nicotine per kg body weight (BW) per min for 30 min) at intervals of 1, 2 and 3.5 h. For validation, blood data of nine subjects after i.v. injection of nicotine (ca. 0.7 μg/kg BW per min for 180 min) were chosen (Fattinger et al., 1997).

For calibration of the oral PBTK model, single and repeated doses (once every 1.5 h for 12 h) of nicotine (4, 8, 12 mg) were ingested orally via a drinking straw (containing loose nicotine bitartrate particles) in a group of 24 smokers (D'Orlando and Fox, 2004). Mean plasma concentrations were calculated from individual nicotine levels presented in the paper. For validation purposes, nicotine-containing capsules coated with a polyacrylic carbomer, Carbopol 974P, (6 and 15 mg) were administered as a single dose to 12 subjects, all non-smokers (Green et al., 1999). Mean experimental serum nicotine concentrations were used from this study.

For calibration of the dermal PBTK model, nicotine patches (Nicolan™) were applied in various doses (15, 30 and 60 mg) directly to the skin of healthy human volunteers (all smokers) for 24 h as single doses and 30 mg applied in repetitive way once every 24 h for 7 days (Bannon et al., 1989). Mean measured plasma nicotine concentrations were published. For validation purposes, single and multiple applications of a nicotine transdermal system (NTS) were investigated on 13 healthy adult male smokers (1.5 mg/h of nicotine released over 24 h) (Gupta et al., 1993). Mean experimental plasma nicotine concentrations were presented.

For calibration of the inhalation PBTK model, cigarettes delivering nicotine doses of 0.4, 1.2, 2.5 mg were smoked (30 per day, with FTC smoking machine) by 12 healthy volunteers (all smokers) (Benowitz et al., 1982). Mean blood nicotine concentrations were measured. For validation, we used the inhalation of 0–64 mg/mL of nicotine by 24 healthy non-smoking subjects (Hansson et al., 1994).

2.2. Experimental data used to develop the PBTD model

The toxicodynamic model of heart rate was developed using data published by Porchet et al. (1988) and validated using experimental results of Fattinger et al. (1997). In both cases, heart rate responses to intravenous nicotine were measured at rest.

To simulate the effect of nicotine on heart rate during exercise, a literature study was chosen in which the effects of nicotine (transdermal 7 mg-nicotine patch) were measured on cycling endurance. The study was carried out on twelve healthy males who were non-smokers (Mündel and Jones, 2006).

2.3. Structure and parameters of the PBTK–TD models

2.3.1. PBTK model

The schematic representation of the PBTK model is shown in Fig. 1. The model consists of three compartments describing: (i) the inhalation process (inhaled and exhaled air linked to the lungs) (Kumagai and Matsunaga, 1995); (ii) the GI tract with 6 sub-compartments (for oral exposure only), Fig. 2; and (iii) the skin with the surface compartment and 4 skin sub-compartments (for dermal exposure only), Fig. 3. The sub-compartments serve to account for the complexity of the absorption process (especially the associated time-lag). Transport through all the organs, except for the skin layers is described by ordinary differential equations.