Nicotine Gum in Thai Smokers with Different CYP2A6 Enzymes: A Population Pharmacokinetic Analysis

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ABSTRACT

Objective: Despite the popularity of nicotine gum in Thailand, population pharmacokinetics of nicotine gum in the Thai population has not been investigated. This study aimed to develop a population pharmacokinetic (POPPK) model of nicotine and to quantify the effects of genetic and non-genetic factors to nicotine pharmacokinetics.

Materials and Methods: Secondary data collected from a previous clinical trial assessing cytochrome P450 2A6 (CYP2A6) genotypes in Thai smokers was investigated. Eighteen participants who had received a single dose of 2 mg nicotine gum were included. Blood samples were collected before, at 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4.5 and 6 hours after nicotine administration. POPPK analysis was performed using nonlinear mixed effect modelling.

Results: One-compartment with 1st order elimination and absorption with 6 transit compartments best described the data. CYP2A6 enzyme activity was a significant covariate on the nicotine clearance. Apparent elimination clearance (CL/F) for a person with 100% CYP2A6 activity was 266.0 L/h. CL/F would be 36.0 L/h in a subject with 0% CYP2A6 activity. However, the impact of non-genetic factors (monthly alcohol consumption, Fagerstrom Test for Nicotine Dependence score and the number of cigarettes per day) on pharmacokinetics of nicotine were not found.

Conclusion: This first report on population pharmacokinetics of nicotine gum in Thai smokers provided the pharmacokinetic model and quantified CL/F for smokers with different CYP2A6 genotypes. A markedly lower exposure to nicotine in the Thai population compared to others highlights the need for more studies to ensure the efficacy of nicotine gum in the Thai population.

Keywords: Population pharmacokinetics; nicotine chewing gum; Cytochrome P-450 CYP2A6 (Siriraj Med J 2024; 76: 504-513)

INTRODUCTION

Tobacco related health problems are serious and rampant in the world today, especially in Thailand. According to a WHO report in 2018, tobacco related deaths accounted for 18% of all deaths in Thailand.[1] Quitting smoking has been shown to substantially reduce mortality rates.[2] Nicotine replacement therapy (NRT), the first-line pharmacotherapy for smoking cessation, is widely used to aid smoking cessation. NRT reduces cravings and relieves nicotine withdrawal symptoms. Without NRT, a successful quit rate of 11.34% was achieved following 6 months of cessation counseling with

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or without sodium nitrate mouthwash.[3] Providing NRTs increased the successful quit rate by 50-60%.[4] Nicotine gum is one form of NRTs, and it is the most dispensed medicine for smoking cessation in Thai community pharmacies.[5]

Nicotine is a weak base, readily absorbed in basic pH, and widely distributed into body tissues.[6] Nicotine is mainly metabolized via hepatic metabolism mediated by the cytochrome P450 2A6(CYP2A6) enzyme. Substantial variations in plasma levels of nicotine after receiving multiple doses of 2-mg nicotine gum has been reported.[7,8] Several pharmacokinetic studies using a non-compartmental approach have been conducted with nicotine gum.[9-14] Considerable variation in pharmacokinetics of nicotine gum has been found in these literatures. The area under plasma concentration-time curve from initiation to infinity ($AUC_{0\text{-}inf}$) ranged from 11.2 to 36.6 ng*h/ml.[9-14] Apparent elimination clearance (CL/F) of nicotine gum was between 54.7 and 178.6 L/h[9-14], whereas elimination clearance of nicotine in intravenous studies was between 66.6 and 90.0 L/h.[6] Plasma elimination half-life of nicotine was between 2.0 and 7.4 hours.[6,9-14]

CYP2A6, a highly polymorphic gene with more than 40 variants, enzyme activity has been shown to influence the therapeutic efficacy of NRT.[15] CYP2A6 enzyme activity varies with different CYP2A6 genetic allele, which has been shown to affect the nicotine metabolism rate and the efficacy of NRTs. Variability in therapeutic responses to NRT was found in groups of different nicotine metabolizers. Providing personalized pharmacotherapy might increase the rate of successful smoking cessation and improve the efficacy of NRT.[16]

Population pharmacokinetic analysis is used to identify sources of variation in a population leading to individualized pharmacotherapy. Although some non-compartmental pharmacokinetic analyses of nicotine gum have been reported, there are limited population pharmacokinetic studies of nicotine following administration of different preparations of nicotine including nicotine gum.[17,18] However, that study did not investigate a Thai population. The objectives of this study were to develop a population pharmacokinetic model of nicotine in adult Thai smokers with different CYP2A6 enzyme activities after administration of nicotine gum and to quantify the effects of genetic and non-genetic factors on the pharmacokinetics of nicotine.

MATERIALS AND METHODS

Study design

This retrospective population pharmacokinetic analysis was performed on secondary data collected from a previous clinical trial investigating CYP2A6 genotypes in Thai smokers at King Chulalongkorn Memorial Hospital, Bangkok, Thailand in 2014-2016 (the trial has not been published, the registration link: https://www.thaiclinicaltrials.org/show/TCTR20161227002). All subjects provided written informed consents. This study was approved by the Institutional Review Board of the Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand (Approval number 085/58).

Study population

The previous clinical trial was divided into 2 parts: CYP2A6 genotyping and pharmacokinetics of nicotine. In the part of the pharmacokinetic study, eighteen participants were recruited. There were 18 adult Thai smokers (10 normal and 8 slow metabolizers) who smoked every day in the 5 months prior to the study with an average of approximately 10 cigarettes per day were selected to investigate the pharmacokinetic profile following single administration of 2-mg nicotine gum. Subjects who were consuming food or drugs that were CYP2A6 inducer or inhibitors, subjects who had a history of chewing disorders or abnormalities in jaw joints, subject with liver or kidney insufficiencies and pregnant and breast-feeding women were excluded.

Sampling schedule and nicotine bioanalysis

Subjects were directed to abstain from any form of nicotine for 12 hours prior to the study and to refrain from any sour juice for 30 minutes before the study. A 2-mg nicotine gum (Nicotinell®, Fertin Pharma A/S, Denmark) was administered orally and chewed as instructed for 30 minutes. Blood samples were collected before the administration of nicotine gum (pre-dose) at 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4.5 and 6 hours after the start of nicotine administration.

Nicotine plasma concentrations were determined by a validated LC-MS/MS using liquid-liquid extraction from the previous clinical trial (the trial has not been published.) The calibration curve ranged from the lower limit of quantification (LLOQ) of 0.25 ng/ml to 50.00 ng/ml. The intra-day and inter-day accuracy and precision were carried out for low (0.75 ng/ml), medium (15.00 ng/ml) and high concentrations (30.00 ng/ml). The accuracy ranged from 92.80% to 103.20% and the precision (% CV) did not exceed 7.80%.

Pharmacokinetic modelling

The population pharmacokinetic model of nicotine was developed using non-linear mixed effect modelling approach as implemented in the NONMEM software,

version 7.3.0 (ICON Development Solutions, Ellicott city, MD, USA).[19] The NONMEM runs were executed by PDx-Pop version 5.2.1 (ICON Development Solutions, Ellicott city, MD, USA). Data checkout and model diagnostics were performed via the software Xpose (version 4).[20]

The first-order conditional estimation method with interaction (FOCE-I) was used throughout the model building process. One- and two- compartment linear models were explored to describe the distribution of nicotine. Various kinds of absorption models including zero-, first-, mixed zero- and first-order absorption, first-order absorption with fixed transit compartments and Weibull-type absorption model were tested to model the absorption of nicotine from buccal mucosal membrane. Pre-dose concentration of nicotine was measurable in 11 subjects and was modelled by a decreasing mono-exponential term as described in literature.[16] Different error models including additive, proportional, combined additive and proportional, and exponential models were tested for residual unexplained variability. Exponential function was used to model inter-individual variability (IIV). Base model was evaluated by examining the basic goodness-of-fit plots, precision of parameter estimates, objective function value (OFV), and akaike information criterion (AIC).

Covariate analysis was performed using a stepwise approach. In the forward addition step, a decrease in OFV of >3.84 ($\chi^2_{0.05}$) was considered significant. In the backward elimination step, an increase in OFV of >10.83 ($\chi^2_{0.001}$) was necessary to retain the covariate in the model. Depending on the relationship between pharmacokinetic parameters and covariates, linear, power, exponential and piece-wise covariate models were evaluated.

The effect of CYP2A6 genetic polymorphism on the clearance of nicotine were evaluated in two different ways; Groups of CYP2A6 phenotype (normal metabolizers and slow metabolizers) as a categorical covariate or activity of CYP2A6 genotype (%) as a continuous covariate which is defined as the following equation.

Activity of CYP2A6 genotype (%) = (AS of genotype/AS of full-function genotype) *100 … (*Equation 1*)

The activity score (AS) was assigned to each CYP2A6 genotype based on known enzymatic activity of CYP2A6 variants as described in previous literature.[21] We transformed AS of each genotype into a percentage value to facilitate the model estimation. Monthly alcohol consumption, Fagerstrom Test for Nicotine Dependence (FTND) score, and number of cigarettes per day were investigated as categorical covariates on clearance of nicotine. The impact of body weight and body mass index on volume of distribution of nicotine were also studied.

The final model was evaluated by bootstrap analysis and with a prediction-corrected visual predictive check.[22,23] Parameter precision was evaluated via bootstrap techniques using 1,000 replicate datasets produced from the final model to determine 95% confidence intervals (CI) of each parameter. Predictive performance of the model was evaluated with visual predictive checks. The magnitude of eta shrinkage (shrinkage in empirical Bayes estimates) and epsilon shrinkage (shrinkage in individual predictions) was investigated to evaluate the informative value of individual data.[22]

RESULTS

A summary of patient characteristics was presented in Table 1. All subjects were male with a median age of 33 years. Six different CYP2A6 genotypes were included in the study. Subjects with a full-function CYP2A6 genotype *1/*1were defined as normal metabolizers. The remaining CYP2A6 genotypes had decreased enzyme activity and therefore subjects with decreased enzymatic activity were defined as slow metabolizers. The enzymatic activity of CYP2A6 genotypes ranged from 0% to 100%. After exclusion of 8 concentrations below the limit of quantification (~4%, 7 concentrations were at time 0 and 1 concentration was at time 6), 172 concentrations were available to develop a population pharmacokinetic model.

Structural model

A two compartment model did not converge successfully and was not used. A one compartment model with 1st order elimination adequately described the observed data. First order absorption with 6 transit compartments was superior compared to all other investigated absorption models (ΔOFV= -35.9 and -10.3 in compared with 1st order absorption and zero-order absorption, respectively). The addition of more transit compartments did not improve the fit. Weibull, serial first-order, and mixed zero- and first-order absorption models did not converge successfully and were not used. Due to high variability during the absorption phase, the first-order absorption rate constant could not be appropriately estimated (the 95%CI for IIV contains zero) and was fixed to the estimated population value of 2.9 h^{-1}, based on model fit. The robustness of the fixed value was verified using a sensitivity analysis by varying the value from1.8 to 4.4 h^{-1}; the variance model parameter values indicated the chosen value of 2.9 to be appropriate. A proportional error model was chosen to describe the residual variability based on suitability or plausibility of parameter estimates.

TABLE 1. Patient characteristics.

Characteristics	Value (N = 18) Median (minimum-maximum)
Age (year)	33.0 (26.0-58.0)
Body weight (kg)	70.5 (57.0-112.0)
Body Mass Index (kg/m^2)	24.6 (19.7-37.9)
Years of smoking (year)	15.5 (8.0-34.0)
Enzymatic activity of CYP2A6 genotypes (%)	100.0 (0-100.0)
	No. (%) of patients
CYP2A6 genotypes	
*1/*1 (AS 2.0 or 100% enzyme activity)	10 (55.5%)
*1/*9 (AS 1.5 or 75% enzyme activity)	1 (5.6%)
*1/*4 (AS 1.0 or 50% enzyme activity)	2 (11.1%)
*9/*9 (AS 1.0 or 50% enzyme activity)	3 (16.7%)
*4/*9 (AS 0.5 or 25% enzyme activity)	1 (5.6%)
*4/*4 (AS 0 or 0% enzyme activity)	1 (5.6%)
Monthly alcohol consumption	
Yes	5 (27.8%)
No	13 (72.2%)
Number of cigarettes per day	
≤10	16 (88.9%)
11-20	2 (11.1%)
	No. (%) of patients
FTND score	
Very low (0-2)	9 (50.0%)
Low (3-4)	7 (38.9%)
Medium (5)	-
High (6-7)	2 (11.1%)
Very high (8-10)	-

Abbreviations: AS = activity score of CYP2A6 genotype, FTND = Fagerstrom Test for Nicotine Dependence score

Covariate model

Modelling clearance as a linear function of activity of CYP2A6 genotypes (%) improved the model fit significantly (ΔOFV= -17.2, p<0.001) and reduced IIV of apparent elimination clearance from 64.9% to 38.5%. Other tested covariates were found not significant. The final elimination clearance is described in equation 2.

CL/F (L/h) = 266.0 + 2.3*(Activity of CYP2A6 genotype (%) -100) … (*Equation 2*)

Model evaluation

Parameter estimates of the final model are presented in Table 2. Fixed effect parameters were estimated with high precision with relative standard errors (%RSEs)

TABLE 2. Population pharmacokinetic parameters of final model.

Parameter	Parameter Description	Estimate [%RSE]	Bootstrap (n=991) Median	95%CI	Shrinkage (%)
Fixed effect					
Apparent elimination clearance (CL/F) = TVCL/F + θ_{CYP2A6} * (CYP2A6-100)					
TVCL/F (L/h)	CL/F for a typical male subject with 100% CYP2A6 enzyme activity	266.0 [10.7]	271.0	219.0 - 348.0	-
θ_{CYP2A6}	Proportional constant of median-normalized CYP2A6 enzyme activity	2.3 [12.6]	2.4	1.1 - 3.6	-
V/F (L)	Population apparent volume of distribution	851.0 [10.3]	863.0	703.0 - 1050.0	-
KA (h^{-1})	Population first-order absorption rate constant	2.9 *fix*	-	-	-
MTT (min)	Population mean transit time	7.2 [15.6]	7.2	4.8 - 10.2	-
C0 (ng/ml)	Population pre-dose concentration	0.6 [18.8]	0.6	0.4 - 0.9	-
Random effect (CV%)					
IIV of CL/F	Interindividual variability for CL/F	38.5 [43.3]	37.1	14.8 - 53.9	3.9
IIV of V/F	Interindividual variability for V/F	38.1 [29.7]	37.2	23.7 - 49.4	4.8
IIV of MTT	Interindividual variability for MTT	54.1 [34.0]	53.5	0.2 - 87.0	15.2
IIV of C0	Interindividual variability for C0	73.1 [22.6]	73.2	50.7 - 96.1	4.2
RUV	Residual unexplained variability	14.7 [26.3]	14.8	10.5 -18.4	18.2
Secondary parameters		**Median (minimum-maximum)**			
C_{max} (ng/ml)	Maximum plasma concentration	1.8 (1.1-4.5)			
t_{max} (h)	Time to reach C_{max}	1.5 (1.0-2.0)			
AUC_{0-6} (h*ng/ml)	Area under plasma concentration-time curve from initiation to last sampling time	6.6 (3.1-21.4)			
AUC_{0-inf} (h*ng/ml)	Area under plasma concentration-time curve from initiation to infinity	8.7 (3.3-57.2)			
$t_{½}$ (h)	Elimination half-life	2.9 (1.3-7.9)			

Coefficient of variation (CV%) of inter-individual variability and residual variability was calculated as $((\exp(\text{variance})-1)^{1/2}) * 100$. Relative standard errors (%RSE) were presented as 100*(standard deviation/mean). The 95% confidence interval (CI) was given as the 2.5th to 97.5th percentiles of bootstrap estimates.

between 10% and 20%. The goodness-of-fit plots did not show any obvious model misspecification (Supplementary Fig 1). However, a small deviation was found at higher concentrations, which was contributed by substantially higher plasma concentrations of subjects who had the complete lack of CYP2A6 enzyme activity. Final parameter estimates of the model were within the 95% confidence interval of the range of estimated obtained from 1,000 bootstrapped datasets, which indicated a stable and appropriate model (Table 2). Value of eta and epsilon shrinkage were within acceptable limits (3.9-18.2%).[22] Prediction- corrected visual predictive checks are presented in Figure1 showing a good predictive performance of the model.[23]

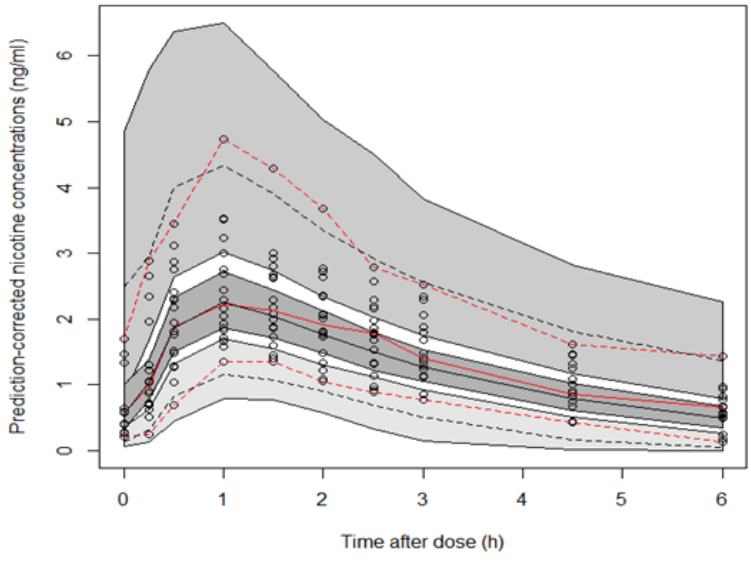

Fig 1. Prediction-corrected visual predictive check of the final model.

Open circles represent the prediction-corrected observed concentrations of nicotine. The black dashed line at the top, black solid line, and black dashed line at the bottom represent 97.5th, 50th and 2.5th predicted percentiles respectively. Observed 97.5th, 2.5th and 50th percentiles are presented as red dashed lines and red solid lines. Shaded areas represent 95% prediction intervals.

DISCUSSION

To date there are limited population pharmacokinetic studies of nicotine, which includes nicotine gum, published in literature.[17,18] It was difficult to directly compare the results of the present study with the previous studies because of differences in study designs. The previous studies developed a population pharmacokinetic model for nicotine following different NRTs (2-mg nicotine gum and 1-mg nicotine nasal spray) and tobacco products (tobacco heating system and cigarette) administration.[17,18]

In the present model, a first-order absorption with a transit compartment model best described the absorption characteristics of nicotine gum whereas a zero-order absorption model did well in the Marchand study[17] and first order absorption in Gisleskog study.[18] It should be noted that Marchand investigated only zero- and first- order absorption models and did not test a transit compartment model. Moreover, there were different formulations between studies (Nicotinell in this study and Nicorette in Marchand and Gisleskog study). These might be part of the reasons for the discrepancy in absorption model. Longer blood collection period (24 hours) in the Marchand study might contribute to the discrepancy in the number of distribution compartments between the two studies: one-compartment in the present study and two-compartments in Marchand study.[17]

Apparent volume of distribution (V/F) of nicotine in a Thai population was 851.0 L, which is higher compared to most values found in literature (V/F=322.0-833.0 L in non-compartmental pharmacokinetic analyses of 2-mg nicotine gum[9-14] and steady state V/F=241.0 L in Marchand study[17]). CL/F for a typical person who had 100% CYP2A6 enzyme activity was 266.0 L/h in the current study, which was approximately 7 times higher than that in the Marchand study[17] and approximately 4 times higher than the Gisleskog study[18], and was also higher than the most values found in the NCA studies of nicotine gum (CL/F=54.7-178.6 L/h). However, it is notable that none of the studies included data on CYP2A6 polymorphism. The elimination half-life of nicotine in the present study (2.2 h) is consistent with the value reported in literature. This suggests a lower bioavailability in Thai population compared with other population. It should be noted that different brands of 2-mg nicotine gum were used in this study and previous studies (Nicorette®).[9-14,17]

The CYP2A6 enzyme is major metabolizing enzyme of nicotine and the CYP2A6 polymorphism has a significant impact on metabolism of nicotine.[6,16] Different CYP2A6 genetic variants result in variation in CYP2A6 enzyme activity, which affects the nicotine metabolism rate. The influence of CYP2A6 polymorphism on CL/F of nicotine was investigated in two different ways; groups of CYP2A6 phenotype as a categorical covariate or activity of CYP2A6 genotype (%) as a continuous covariate. We found that the inclusion of activity of CYP2A6 genotype (%) significantly improved the model fit (ΔOFV= -17.2, $p<0.001$) and reduced IIV of CL/F from 64.9% to 38.5% which were better than the inclusion of groups of CYP2A6 phenotype (ΔOFV= -7.8, $p<0.05$; IIV of CL/F reduced from 64.9% to 51.5%). Therefore, CYP2A6 activity (%) was chosen as a significant covariate to explain the impact of CYP2A6 polymorphism on IIV of CL/F.

According to final model described in equation 2, if the CYP2A6 activity decreased 25.0%, the CL/F decreased by 57.5 L/h (or 21.6%). Positive relationship between CL/F of nicotine and CYP2A6 activity was consistent with previously reported data.[17] However, the results need to be interpreted with caution because different methods of CYP2A6 activity measurement might affect the results. Nicotine metabolite ratio (NMR) has been reported as a valid indicator of CYP2A6 activity.[24] Unfortunately, NMR data was not available and activity score system was used to predict CYP2A6 activity based on known enzymatic activity of CYP2A6 variants. However, it is worth noting that the activity score system is also a valid, easy-to-use tool to predict phenotype and is utilized to provide genotype-based dosing recommendation in clinical settings.[25,26]

It has been reported that smoking itself inhibited the metabolism of nicotine.[6] Therefore, we investigated the impact of the number of smoking years and the number of cigarettes per day on CL/F. None of these covariates were significant, consistent with findings in a previous study.[17] Further, Dermody et al[27] and Gubner et al[28] have reported that an association between alcohol consumption and rate of nicotine metabolism, but we did not find a significant effect of monthly alcohol consumption on CL/F. The reason could be that the previous two studies included chronic heavy drinkers diagnosed with alcohol dependent disorder, while only 5 out of 18 individuals in the current study consumed between 5 and 50 glasses of alcoholic beverages per month and alcohol dependent disorders were not present. A larger sample size, with various smoking and alcohol consumption history is needed to examine these associations.

Despite a 12-hour washout period, plasma concentrations of nicotine were measurable before dosing. This has also been seen in previous studies.[10,14,17] The presence of pre-dose concentrations could interfere with the estimation of the pharmacokinetic parameters of nicotine. Different approaches to handle the baseline data have been studied.[29] Among them, estimating the typical value and IIV of baseline concentrations provided the best performance, with less bias and less imprecision compared to other methods.[29] Therefore, typical value and IIV of pre-dose concentrations were estimated in this study. Then, pre-dose concentrations were modelled as mono-exponential decay as described in literature.[17] Addition of pre-dose model into the base model provided the better model fit in every aspect of absorption models and RUV models (Supplementary table 1).

There are some limitations in this study. First, this was a retrospective analysis performed on secondary data with a small sample size, the result validity may be distrustful, however, the study has demonstrated a crucial trend of CYP2A6 genotypes effects on drug elimination in Thai smokers. This study analyzed only Thai smokers' data, therefore the results from this study might not represent other populations. Second, all subjects were male. It has been reported that clearance of nicotine is higher in females than in males.[6,17] We could not investigate that factor in this study. However, it is worth noting that the prevalence of smoking is about 15-20 times higher among men than women in Thailand.[30] Third, due to the secondary data analysis, the details of collected data (monthly alcohol consumption, FTND score, and number of cigarettes per day) were not enough to analyze as continuous data, it might be one of the reasons why we have not found some significant relation between these covariates and pharmacokinetic parameters. Finally, the 6-hour sampling time was relatively short and might affect the characterization of the elimination phase.

Despite limitations, to the best of our knowledge, this is the first population pharmacokinetics of nicotine gum in a Thai population. Comparison of pharmacokinetic parameters of plasma nicotine from both compartmental and non-compartmental analysis of single-dose 2-mg nicotine gum in non-Thai population versus Thai population was shown in Table 3. Interestingly, exposure of nicotine after chewing nicotine gum is substantially lower in Thai population compared to non-Thai population. This observation might challenge the therapeutic efficacy of current dosage regimen of nicotine gum for Thai population. Therefore, the efficacy of current dosage regimen should be confirmed by further studies. Moreover, studies with a larger sample size and more frequent sampling design are recommended to better characterize the pharmacokinetics of nicotine gum.

CONCLUSION

The pharmacokinetics of nicotine in Thai population after nicotine gum administration was best described by a linear one-compartment disposition model with first-order absorption and 6 transit compartments describing the absorption phase. The enzymatic activity of different CYP2A6 genotypes influences the nicotine clearance. Providing personalized smoking cessation based on CYP2A6 genetic variation is important to optimize therapeutic efficacy of nicotine medications. However, the impact of non-genetic factors like monthly alcohol consumption, FTND score and number of cigarettes per day on pharmacokinetics of nicotine were not found in this study. Moreover, this study highlights a substantially lower exposure of nicotine in Thai population compared

TABLE 3. Comparison of pharmacokinetic parameters of plasma nicotine after administration of single dose 2-mg nicotine gum in non-Thai population versus Thai population.

NCA											**POP PK**
Author (year)	Choi (2003)[a]	Dautzenberg (2007)	Muneesh (2016)	Hansson (2017)[a]	Brossard (2017)[b]		Du (2018)	This study		Marchand (2017)[b]	This study
Population	USA	French	Indian	Swedish	Japanese		European	Thai		Japanese	Thai
N	23	9	43	44	18 (Tokyo)	18 (Saitama)	62	10 (Normal metabolizer)	8 (Slow metabolizer)	36	18
Blood sampling	14 samples over 12 h	11 samples over 8 h	19 samples over 24 h	19 samples over 12 h	16 samples over 24 h		13 samples over 12 h	10 samples over 6 h		16 samples over 24 h	10 samples over 6 h
C_{max} (ng/ml)	4.0 ± 1.5	2.9 ± 1.2	7.3 ± 2.1	5.9 ± 1.9	4.8	7.52	3.7 ± 1.3	2.53 ± 1.80	3.15 ± 0.47	5.7	1.8 (1.1-4.5)
T_{max} (h)	0.8 ± 0.2	0.8 ± 0.1	0.7 (0.3,3.0)	0.5[c]	0.6[d]	0.8[d]	0.8 (0.5, 1.5)	0.80 ± 0.13	1.50 ± 0.13	0.8	1.5 (1.0-2.0)
$AUC_{0\text{-last}}$ (h*ng/ml)	10.7 ± 6.6	10.6 ± 4.4	32.3 ± 11.5	15.1 ± 5.3	14.9	27.9	10.2 ± 3.78	8.30 ± 0.77	13.32 ± 2.45	21.3	6.6 (3.1-21.4)
$AUC_{0\text{-inf}}$ (h*ng/ml)	11.3 ± 7.6	13.8 ± 5.6	36.6 ± 13.4	17.1 ± 6.0	16.6	31.1	11.2 ± 4.0	11.23 ± 1.41	24.63 ± 7.03	27.0	8.7 (3.3-57.2)
$t_{1/2}$ (h)	2.5 ± 1.2	2.5 ± 1.0	7.4 ± 4.7	2.9[c]	4.8	3.5	2.0 (1.2, 4.2)	2.59 ± 0.30	4.22 ± 0.63	0.8*, 11.97	2.9 (1.3-7.9)

Values were expressed as Mean ± SD or Median (minimum, maximum). NCA = non-compartmental pharmacokinetic analysis;
POP PK = population pharmacokinetic analysis; C_{max} = maximum plasma concentration of nicotine; t_{max} = time to C_{max}; $AUC_{0\text{-last}}$ = area under plasma concentration-time curve from initiation to last sampling time; $AUC_{0\text{-inf}}$ = area under plasma concentration-time curve from initiation to infinity; $t_{1/2}$ = plasma elimination half-life; *distribution half-life. [a] Plasma concentrations of nicotine were reported as baseline-adjusted values because of measurable pre-dose concentrations. [b] Values were expressed as geometric means. [c] Value was expressed as mean. Standard deviation was not reported. [d] Value was expressed as median. Range was not reported.

to other populations, which emphasizes the need of more study to ensure the efficacy of nicotine gum in Thai population.

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