Population Pharmacokinetic–Pharmacodynamic Model of Craving in an Enforced Smoking Cessation Population: Indirect Response and Probabilistic Modeling[1]

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Purpose. A population pharmacokinetic–pharmacodynamic model accounting for placebo effect was used to relate nicotine concentration and enforced smoking cessation craving score measured by the Tiffany rating scale short form.

Methods. Twenty-four smokers were enrolled in a placebo-controlled, randomized, double-blind, three periods, crossover trial. The study objective was to describe the nicotine-induced changes on craving scores. Two modeling strategies based on a mechanistic (indirect response models with drug-related inhibition on the k_{in} synthesis rate and with a drug-related stimulation of the k_{out} removal rate were evaluated) and a probabilistic (logistic regression) approach were used.

Results. Placebo response model properly fitted the circadian changes on craving scores. The analysis revealed that the indirect response model with inhibition on k_{in} was the preferred model for the smoking data whereas the preferred model for the Nicotine Replacement Therapy data was the one with stimulation on k_{out}. The logistic analysis showed that the nicotine concentration was a significant predictor of reduction in craving during the free-smoking period.

Conclusions. Nicotine dosage regimen can influence the nicotine mechanism of action: an instantaneous delivery at an individually selected time seems to inhibit the onset of craving while constant delivery at a pre-defined time seems to attenuate the craving.

KEY WORDS: smoking cessation; craving; nicotine; Tiffany scale; population PK/PD; indirect response models; logistic regression; NONMEM.

INTRODUCTION

Finding effective methods of smoking cessation challenges health care professionals to explore innovative approaches to treating nicotine addiction because the vast majority of smokers report wanting to quit smoking (1). Pharmacological aids have become central in smoking cessation treatment and Nicotine Replacement Therapy (NRT) has been proven to be one of the reference treatments (2,3). Smokers attempting to quit often complain of an urge and craving to smoke. Urge and craving have been identified as prominent features of the tobacco withdrawal condition and frequently are posited to be major contributors to the high rate of relapse encountered in many treatment programs of smoking cessation. A specific questionnaire, the Tiffany rating scale, has been developed and validated to quantify the degree of smoking urges (4). The objective of the present study was to investigate the possible relationship between saliva nicotine concentration and the intensity of craving as quantified by the Tiffany scale. A placebo-controlled, randomized, double-blind, three periods, crossover trial was designed to investigate the possible relationship between Tiffany Craving scores and saliva nicotine concentrations in a population of 24 smokers. Initially, the Tiffany scores collected over 72 hours were analyzed using a conventional ANOVA (allowing for subject, period, and treatment effect) without accounting for the values of nicotine concentration. This analysis revealed a statistically significant difference between the average scores observed after the placebo and smoke sequence (mean values of 4.5 and 3.6), and between placebo and NRT (mean values of 4.5 and 3.8). The average nicotine levels measured after smoke and NRT were of 398 ng/ml and 178 ng/ml. On the basis of these findings, it was decided to investigate the possibility to define deterministic and probabilistic models suitable to predict the changes on Tiffany score as a function of the nicotine concentrations.

MATERIAL AND METHODS

Subjects

Twenty-four healthy subjects (20 men and four women) free from clinically significant illness or disease as determined by their medical history (including family history), physical examination, laboratory data, and other tests were enrolled in this study. The subjects ranged in age from 19 to 52 years (26.9 ± 9.3) with a body weight ranging from 50 to 85 kg (69.3 ± 9.0). According to the study protocol, only smokers of 15 cigarettes or more a day for the past year (not motivated to stop smoking), with a self reported dependence (5) to tobacco smoking (Fagerstrom Tolerance Questionnaire score of at least 7) and free from current use of any NRT were enrolled in the study. One subject dropped out from the study; therefore, 24 subjects were analyzed in the placebo group whereas only 23 subjects were used in the analysis of the treated groups.

Study Design

This was a double-blind, according to the non-smoking sessions, randomized, placebo-controlled, three periods crossover study. At three different periods, each subject received NRT, a placebo, and was allowed to smoke, according to the randomization code. In two periods, smoking was forbidden to subjects who received NRT and placebo then, in the third period, the subjects were allowed to smoke. Each study period consisted of 72 hours with a free-smoking washout of at least 10 days. The Tiffany questionnaire was collected at 0, 3, 6, 12, 24, 30, 36, 48, 54, 60, and 72 hours and, at the same times, saliva samples were collected for nicotine measurement. Subjects received: (a) NRT, given as a nicotine patch (Nicotinell® 30 cm^2; 52.5 mg, delivery 21 mg/24 hours) every 24 hours; (b) NRT Placebo, given as a nicotine placebo patch

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every 24 hours. Nicotine and placebo patches were placed at 24-hour intervals starting at 11:00 p.m. the evening before the beginning of smoking deprivation, then replaced at the same time on the first, second and third day. The individual saliva nicotine concentration values measured in the NRT and smoking periods are displayed in Figure 1.

Nicotine Assay

Nicotine analysis of saliva samples was performed using a high performance liquid chromatography method combined with mass spectrometric detection. The precision and accuracy of the method were evaluated using the results of the quality control samples (QCs) assayed daily with the clinical samples. The precision of the QCs were smaller than 14.4% at low level, 11.1% at medium level, and 12.6% at high level of the compound. The accuracy of the QCs averaged –5.71% at low level, –12.0% at medium level and –5.31% at high level of nicotine.

Modeling Approaches

Two independent modeling approaches have been used. The first approach was based on a mechanistic model describing the nicotine-induced fluctuation of the craving scores observed after placebo. The second one was based on the estimate of the probability for a predefined clinical outcome (defined as a percentage of reduction on the placebo response) for a given nicotine level. The expected outcome was arbitrarily fixed to a reduction of 20% of the craving score in presence of nicotine, considering that the largest effect observed was in average a reduction of 20% (from 4.5 to 3.6).

Indirect Response Model Approach

The basic premise of this approach is that a measured response (R) to a drug (or placebo) may be produced by indirect mechanism (6). The factors controling the input or production (k_{in}) of the response variable may be either inhibited or stimulated and the determinant of loss (k_{out}) of the response variable may be either inhibited or stimulated.

Placebo Effect Model

The rate of change of the response over time with no drug present was described by:

$$\frac{dR}{dt} = k_{in} - k_{out} R \quad (1)$$

where k_{in} represents the zero-order constant for production of the response and k_{out} defines the first-order rate constant for loss of the response.

As stationarity is assumed, the response variable (R) begins at an average baseline (Ro_{Plac}), changes with time, and returns to (Ro_{Plac}). Thus:

$$k_{in} = k_{out} Ro_{Plac} \quad (2)$$

which reduces the number of parameters in the model. Inspection of the score changes over time after placebo administration indicates the presence of a circadian variability; therefore k_{in} was modelled as a cosine function:

$$k_{in} = k_{out} Ro_{Plac} \cdot \left(1 + \text{Amplitude} \cdot \cos\left[(t - t_{max})\frac{2\pi}{24}\right]\right) \quad (3)$$

where Ro_{Plac} is the average placebo response at baseline, Amplitude is the amplitude of the circadian variation, t is the time, t_{max} is the time of the peak response (acrophase) and $2\pi/24$ converts clock time in radians.

Pharmacokinetic–Pharmacodynamic (PK/PD) Model

The aim of the PK/PD model was to relate the changes on nicotine concentrations, due to NRT application and smoking, to the changes on craving scores.

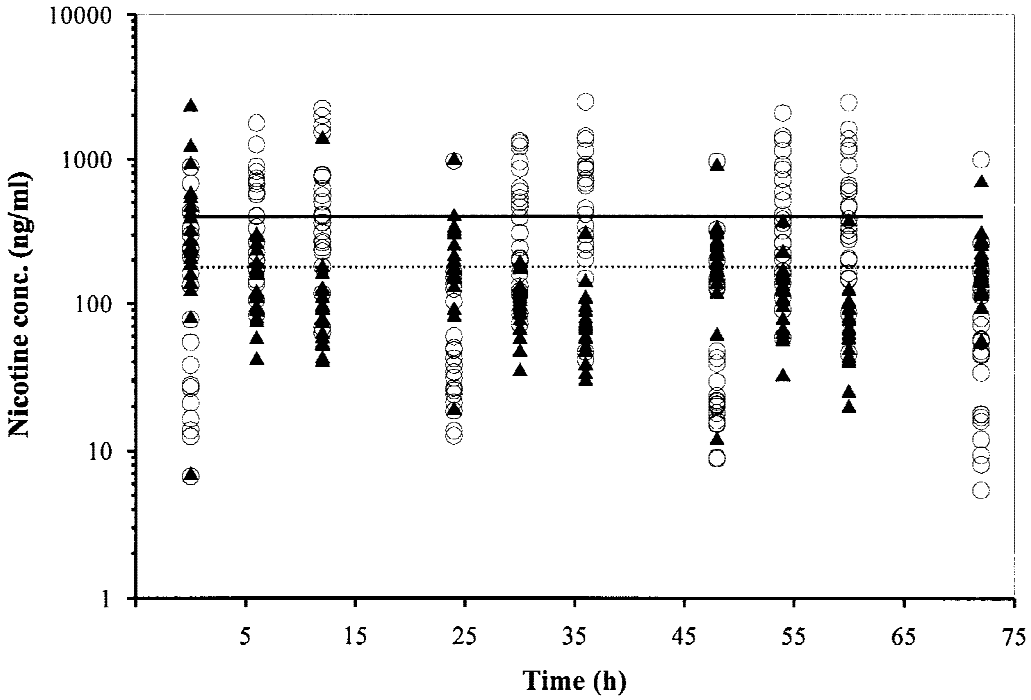

Fig. 1. Time–course of the individual saliva nicotine concentrations in the NRT (▲) and in the smoking (○) period, with the average value of 398 ng/ml for smoking (continuous line) and of 178 ng/ml for NRT (dotted line) periods.

A sequential approach has been applied: the individual placebo response parameters (k_{in}) were initially estimated on the placebo data using empirical bayesian procedure, and the parameters of this model were fixed in the subsequent analyses. In a recent article (7), nicotine was shown to follow circadian pharmacokinetic due to clearance change for meal and time effect. For this reason, a semi-parametric approach was used to model the nicotine concentration fluctuation by approximating the nicotine concentration changes over time (C_{Pest}) using a linear interpolation between two consecutive measured concentrations.

The response pattern showed a marked reduction on craving score in the NRT or smoking period. This finding can equally be accounted by two of the four indirect response models proposed by Dayneka *et al.* (8): the model I with a drug-related inhibition on the k_{in} synthesis rate (Eq. 4) and the model IV with a drug-related stimulation of the k_{out} removal rate (Eq. 5). No prior knowledge was available on the nicotine mechanism of action on craving. Therefore, it was decided to evaluate the two models applied independently to the craving effect induced by nicotine after NRT and after smoking.

$$\frac{dR}{dt} = k_{in} \cdot \left[1 - \frac{I_{max} \cdot C_{Pest}}{IC_{50} + C_{Pest}}\right] - k_{out} \cdot R \quad (4)$$

$$\frac{dR}{dt} = k_{in} - k_{out} \cdot R \cdot \left[1 + \frac{E_{max} \cdot C_{Pest}}{EC_{50} + C_{Pest}}\right] \quad (5)$$

where E_{max} is the maximal stimulation rate, EC_{50} is the nicotine concentration producing 50% of E_{max}, I_{max} is the maximal inhibition rate, IC_{50} is the nicotine concentration producing 50% of I_{max}, C_{Pest} the estimated nicotine concentration, and k_{in} is the placebo effect defined by the Equation 3. All the saliva nicotine concentrations were jointly collected with the Tiffany scale scores, therefore the measured concentration values (Nc) were used for C_{Pest} in the parameter estimation calculation procedure while the interpolated values C_{Pest} were used in the generation of the graphs of the predicted curves. The underlying rationale to this model assumes that the effect on craving score is a monotonic function of saliva nicotine concentration, but the maximum effect (I_{max} or E_{max}) and the concentration producing 50% of the maximal response (IC_{50} or EC_{50}) may vary according to NRT and free smoking. Therefore, the craving scores were independently fitted to the saliva nicotine concentrations collected in the NRT and smoking treatment periods.

Probabilistic Model

An alternative method to evaluate the effect of nicotine on craving is to attribute at each nicotine concentration value a binary score defined as success (change of craving score ≥20%) or failure (otherwise) and then to evaluate the probability that a success occurs as a function of the nicotine concentration value. A logistic model was used to describe the probability to observe a positive outcome. The probability for success was described by the model:

$$\lambda_{ij} = \theta_1 + \theta_2 \cdot Nc + \eta_i \quad (6)$$

$$p_{ij} = \frac{e^{\lambda_{ij}}}{1 + e^{\lambda_{ij}}} \quad (7)$$

where i is the index for subject, j is the index for observation, θ_1 is the intercept of the logistic function, θ_2 is the slope of the logistic function, η_i is the normal distributed random effect on λ_i, and Nc are the measured nicotine concentration values.

DATA ANALYSIS

Population Pk/Pd Analysis

The analyses were performed using the non-linear mixed-effect modeling approach as implemented in the NONMEM (Version V) computer program (9). The population characteristics of the parameters (fixed and random effects) were estimated using the subroutines ADVAN6 from the library of programs provided with the NONMEM–PREDPP package. Intra-subject variability (random effects) were assessed according to an exponential error model associated to each fixed effect parameter: the p_i parameter of the j_{th} subject was described by the relationship:

$$p_j = P_{mean} * \exp(\eta_P) \quad (8)$$

where P_{mean} is the population mean and η_P is assumed to be a random variable with mean zero and valiance $\omega^2\eta_P$. The craving scores in the jth individual were assumed to be affected by an additive error described by the relationship:

$$C_{ij}(t) = f(p_j, C_{Pestij}, t_{ij}) + \varepsilon_{ij} \quad (9)$$

where p_j are the model parameters of the jth subject, t_{ij} is the time of the i_{th} measurement, f is the structural model, and ε_{ij} represents the residual departure of the model from the observations and contains contributions from intra-individual variability, assay error and model misspecification. ε is assumed to be a random variable with mean zero and variance $\sigma^2\varepsilon$. Bayesian estimates of model parameters for each subject were obtained using the 'POSTHOC' option in NONMEM.

Probabilistic Approach

A dummy binary variable taking the value 0 for failure and 1 for success was derived from the observed craving score. The nicotine levels were evaluated as potential predictors of the probability of success in two independent analyses performed on the data collected in the NRT and smoking periods. The nicotine concentration in the NRT or in the smoking periods were considered as statistically significant predictors of the probability of success when the log-likelihood ratio test (see below) revealed a significant improvement in the objective function estimated using the full model defined by the Equation 7 in comparison to reduced model obtained setting θ_2 equal to zero. The analysis was performed using the non-linear mixed effect approach as implemented in NONMEM with the CONDITIONAL and LAPLACIAN estimation options.

Model Selection

The model discrimination between non-nested models, such as the two indirect response models, was performed using the Akaike Information Criterion (AIC): the smaller AIC value was associated to the better model (10). For nested models, the importance of different modeling options, such as the inter and intra-individual distribution (normal or log-normal), and the pharmacodynamic and logistic model structure was evaluated on the basis of the changes on minimum Objective Function (OF). Parameters were added to the model based on an improvement in residual plots and a decrease in the OF which is estimated by NONMEM as –2 times

the log likelihood of the data. The changes in the OF between two nested models is approximately χ^2 distributed with degree of freedom equal to the difference between the number of parameters in the full and reduced model. Thus, a decrease of 4 units in the OF was considered statistically significant ($P < 0.05$) for addition of one parameter.

RESULTS

Population Pharmacokinetic–Pharmacodynamic Modeling

The population database consisted of 253 observations following placebo, 223 following NRT, and 223 following smoking obtained from 23 subjects. The mean and the median saliva nicotine concentration value observed in the NRT period was of 178 ng/ml and 121 ng/ml with the 5^{th} and 95^{th} percentiles equal to 39 and 417 ng/ml, whereas the mean and the median value in the smoke period was of 398 ng/ml and 204 ng/ml with the 5^{th} and the 95^{th} percentiles of 15 and 1353 ng/ml. The population PK/PD analysis was conducted in three steps: in the first one the placebo effect model was fitted to data and the individual posterior parameter estimates added to the population database, in the second and third step the two alternative indirect response models were fitted independently to data collected in the NRT and smoking periods using the individual parameters associated to the placebo effect previously estimated. The goodness of fit was assessed by the analysis of the residuals scatter plot and by comparing the plot of the posterior predicted values versus the observed craving scores to the unitary slope curve. The results of the analysis revealed that the indirect response model with inhibition on k_{in} was the preferred model for the smoking data while the preferred model for the NRT data was the one with stimulation on k_{out}.

In Figure 2, the mean population predicted craving scores curves after placebo, NRT and smoke using the estimates obtained by first-order method of NONMEM are presented. The average baseline value RO_{Plac} estimated in the Placebo analysis was used to draw this figure because the basal values in the three treatment groups did not differ statistically. The final NONMEM fixed and random effect parameter estimates are reported in Table I. The AIC criterion revealed that the model IV, with stimulation on the first order removal rate, better described the relationship between saliva nicotine concentrations and craving in the NRT period while the model I, with inhibition of the zero-order synthesis rate, best fitted the PK/PD relationship between nicotine concentration and craving in the smoking period.

The scatter plots presenting observed versus predicted craving scores for each subject together with the identity line are reported in Figure 3 to illustrate the good agreement between model predictions and observations. Typical posterior individual fittings with observed craving scores and model predicted curves after placebo, NRT, and smoke in three subjects are displayed in Figure 4. The relatively high values of random effect parameters translated both the high inter-individual variability in the placebo average response and the high variability in the relationship between nicotine concentration and the changes on Tiffany scale. The inspection of the goodness of fit criteria indicates that the proposed indirect PK/PD model was appropriate to explain the fluctuation on craving as a function of saliva nicotine concentration. Nicotine in the NRT treatment period appears to produce a pharmacodynamic effect on craving by stimulating the k_{out} dissipation rate according to a E_{max} process with a maximal effect of 0.696 and an EC_{50} of 250 ng/ml. During the smoking period, the saliva nicotine concentrations appear to act on the craving by an inhibitory effect on the synthesis rate with a maximal effect of 0.406 and an IC_{50} of 388 ng/ml.

Probabilistic Modeling

The population database consisted of data collected on 23 subjects. Nicotine concentration values (n = 223) were used in the smoke period with 119 failures (change of craving

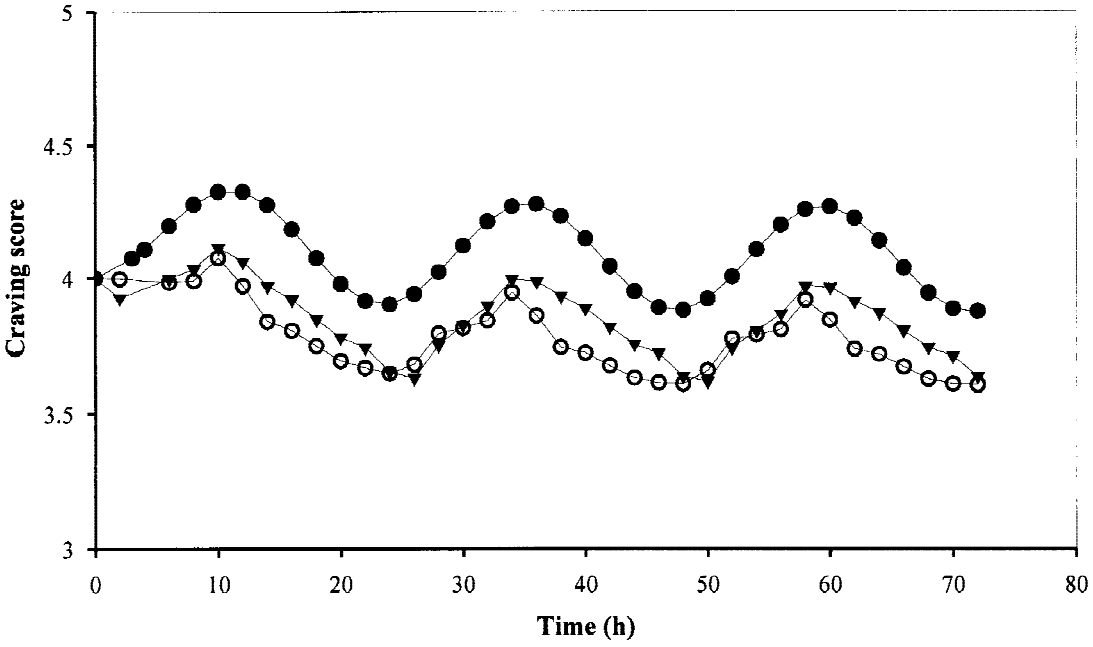

Fig. 2. Mean population predicted craving scores in the Placebo (●), NRT (▼), and smoking (○) treatment period.

Table I. Population Parameter Estimates with Their Estimation Precision (S.E.)[a]

Model	Param.	Fixed effect	Random effect	Residual error	OF	AIC	Preferred model
Placebo	Ro_{Plac}	4.07 (0.281)	0.127 (0.038)	0.185 (0.041)	6.98		
	Amplitude	0.185 (0.053)	3.52 (3.75)				
	t_{max} (h)	7.31 (0.305)	(*)				
	k_{out} (h^{-1})	0.0705 (0.019)	5.75 (3.58)				
NRT							
I	I_{max}	0.192 (0.077)	2.27 (1.87)	0.416 (0.103)	87.47	93.5	
	IC_{50} (ng/ml)	43.3 (32.6)	(*)				
IV	E_{max}	0.696 (0.297)	(*)	0.406 (0.1)	81.97	88.0	✓
	EC_{50} (ng/ml)	250 (90.3)	4.65 (1.78)				
Smoke							
I	I_{max}	0.406 (0.170)	1.15 (1.63)	0.632 (0.162)	189.37	193.4	✓
	IC_{50} (ng/ml)	388 (1.63)	8.49 (10.3)				
IV	E_{max}	0.783 (0.411)	0.748 (0.969)	0.690 (0.160)	197.23	205.2	
	EC_{50} (ng/ml)	580 (371)	4.26 (3.41)				

[a] (*) For these parameters the random effects were not included in the model on the basis of objective function change criteria.

<20%) and 104 success (change of craving ≥20%) while, in the NRT treatment period, 223 nicotine concentration values with 130 failures and 93 success were included in the analysis. The population parameter estimates are displayed in Table II. The results of the analysis revealed that the preferred model was the reduced model in the NRT period while the full logistic model best fitted the data in the smoking period. Therefore, only the nicotine concentrations measured after smoke were retained as a significant predictor for the probability of craving reduction by the log-likelihood ratio test used to evaluate the alternative models.

Figure 5 displays the predicted median probability for the pre-defined outcome as a function of nicotine concentration observed in the smoking treatment period. A confidence band defining the 5th and the 95th percentiles around the predicted probability completes the graph.

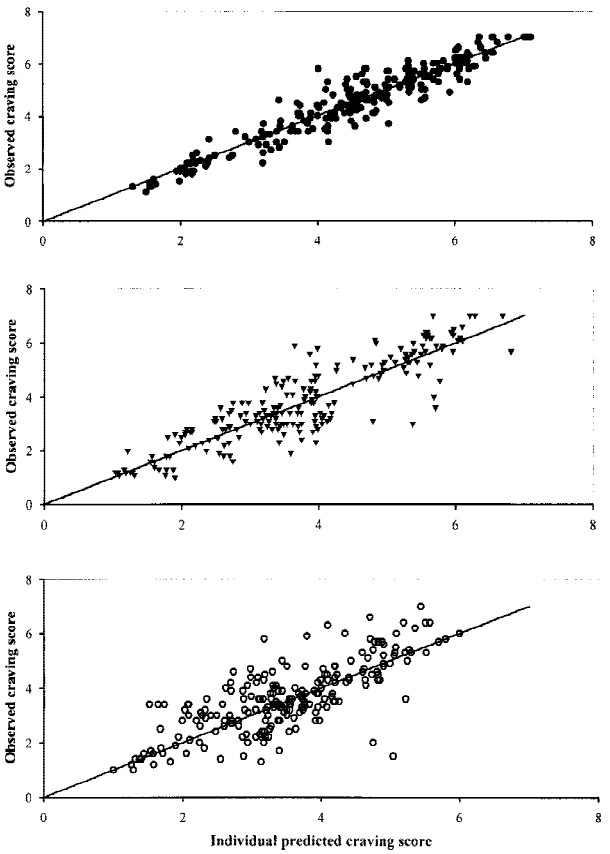

Fig. 3. Observed versus predicted craving scores for each subject in the Placebo (●, top panel), NRT (▼, middle panel), and smoking (○, bottom panel) treatment period.

DISCUSSION

The study confirm previous observations that smoking deprivation generates a monotonic increase in cigarette craving accompanied by a monotonic decrease in blood nicotine levels (11). Furthermore, many clinical smoking cessation trials have demonstrated a connection between plasma nicotine levels and urge to smoke by showing that subjects who received nicotine replacement show less craving than subjects receiving placebos (3,12). A significant negative correlation between the increase of blood nicotine levels and decrease of craving for cigarettes has been recently showed in a population of heavy smokers undergoing forced tobacco abstinence (13). However, the relationship between the temporal changes on craving, measured by the Tiffany scale, and the saliva nicotine concentrations observed after NRT therapy and smoking has never been studied, to our knowledge, in a controlled trial accounting for placebo effect and enforced smoking cessation in a period of 72 hours.

The modeling approach developed in this study was able to describe the variation on craving after placebo according to a circadian model with cycle of 24 hours. The placebo response showed a fluctuation of 0.185 around to a basal value of 4.07 units on Tiffany scale, whereas the highest craving scores were observed at the acrophase time (about 3.30 p.m.). Nicotine was delivered to the subjects enrolled in the study according to different dosage regimens: an immediate release (bolus input) self-administered at subject discretion in the smoking period and a zero order input rate in the NRT period with administrations at pre-defined times. An important result found in this study was that the rate of nicotine delivery and the time of nicotine administration appeared to affect the mechanism of action of this substance. Nicotine appeared to

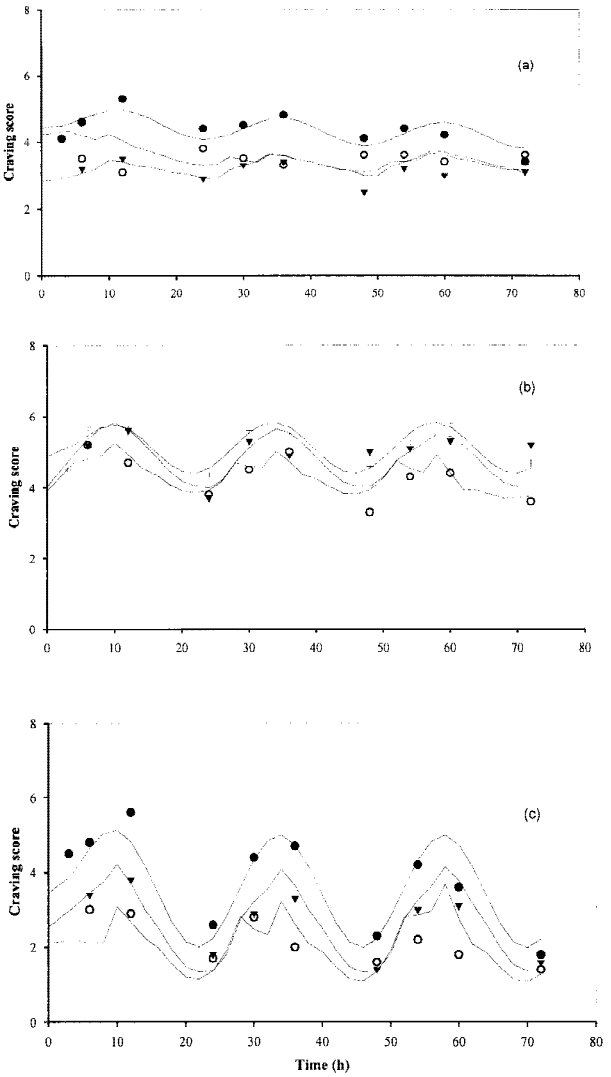

Fig. 4. Posterior individual fit with the observed craving scores of three typical subjects in the (a) placebo (●), (b) NRT (▼) and smoking (c) (○) treatment period.

prevent the full onset and the intensity of craving progression in the smoking period by affecting the k_{in} constant whereas the nicotine delivered in the NRT period appeared to antagonize the progression of the craving intensity by affecting the k_{out} constant in the indirect response model. These findings are consistent with the assumption that the pharmacodynamic response can be differently modulated as a function of the dosage regimen in an indirect pharmacodynamic response (14).

The PK/PD model adequately described the onset, extent, and duration of the pharmacological response for the two treatments. The maximal inhibition I_{max} (0.406) was about 40% lower than the maximal stimulation E_{max} (0.696) value whereas the estimated nicotine concentration giving 50% of the maximal stimulation (250 ng/ml) was about 36% lower than the nicotine concentration giving 50% of the maximal inhibitory effect (388 ng/ml).

According to the E_{max} PD model, the increase on the nicotine concentration necessary to reduce the craving score increases exponentially as the expected reduction approaches

Table II. Logistic Analysis Population Parameter Estimates with Their Estimation Precision (S.E.)[a]

	θ_1	θ_2	ω^2_η	OF	Preferred Model
NRT					
Full model	0.404 (0.413)	0.000607 (0.000535)	2.46 (0.996)	259.539	
Reduced model	0.512 (*)	0	2.45 (*)	260.131	✓
Smoke					
Full model	0.728 (0.348)	–0.00146 (0.000661)	1.76 (1.19)	270.207	✓
Reduced model	0.147 (*)	0	1.47 (*)	284.352	

[a] (*) The program was not able to estimate this value.

the maximal achievable level (E_{max} or I_{max}). For example, the nicotine concentrations after NRT treatment have to be increased from 250 to 1000 ng/ml to increase the effect on craving of 30% (from 50% up to 80% of E_{max}) whereas the nicotine concentrations have to be increased from 1000 to 4749 ng/ml to increase the effect of 15% (from 80% to 95%). These findings suggest that the cost for an improvement of the craving scores above 80% of the maximal achievable effect becomes extremely high in term of nicotine concentrations to be achieved. The logistic analysis showed that the nicotine concentration measured in the smoking period is a significant predictor of the outcome defined as a reduction of at least 20% in the craving score after smoking. However, this was not the case for the nicotine concentrations measured in the NRT treatment period. This apparent discrepancy between the different outcome predictability properties of nicotine concentration in the two treatment periods may probably be connected to the different ranges of concentrations reached in the two periods or to the assumption that the probabilistic modeling approach best describes an inhibitory indirect response pharmacodynamic effect. The interest of the logistic analysis is to estimate the probability of obtaining a defined outcome for each nicotine concentration. For example, the probability of a craving score reduction of at least 20% is equal to 50% for a nicotine concentration of about 500 ng/ml

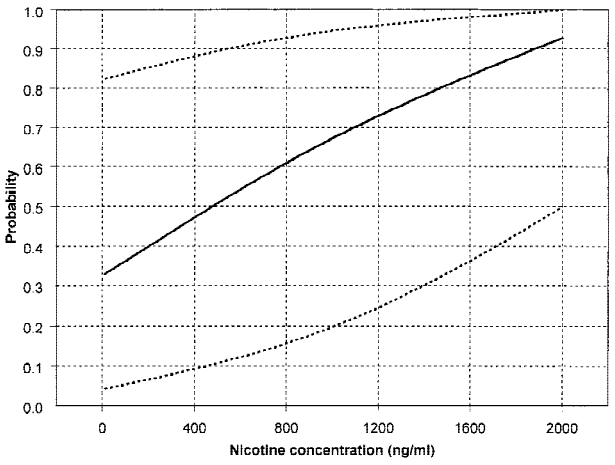

Fig. 5. Median probability of a craving score reduction of at least 20% (solid line) with the 5th and the 95th percentiles (dotted lines).

and to 80% for a nicotine concentration of about 1500 ng/ml. Finally, the indirect modeling approach adequately described the onset, extent, and duration of the craving after NRT and smoke while the logistic model was able to estimate the probability of a given outcome in respect of nicotine concentrations.

In conclusion, we believe that the modeling exercise presented in this article can profitably contribute to formulate reasonable assumptions, but not to supply any formal proof, of the nicotine action mechanism. Specific trials have to be designed at this purpose. On the basis of the present study, we can reasonably support the assumptions that craving is strictly related to saliva nicotine concentrations and that the delivery rate of nicotine can influence the nicotine mechanism of action: an almost instantaneous delivery at an individually selected time would inhibit the full onset and the progression of craving intensity while, constant delivery at a pre-defined time of a day would attenuate the craving intensity over time. However, further experiments have to be conducted to verify and validate the suggested nicotine mechanism of action due to sparse nature of the observations available (10 measurements over 72 hours per subject) and the limited number of subjects enrolled in this trial.

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REFERENCES

1. US Centers for Diseases Control and Prevention. Cigarette smoking among adults—United States 1993. *MMWR* **43**:925–929 (1994).
2. J. L. Tang, M. Law, and N. Wald. How effective is nicotine replacement therapy in helping people to stop smoking? *BMJ* **308**:21–26 (1994).
3. M. C. Fiore, S. S. Smith, D. E. Jorenby, and T. B. Baker. The effectiveness of the nicotine patch for smoking cessation: A meta-analysis. *JAMA* **271**:1940–1947 (1994).
4. S. T. Tiffany and D. J. Drobes. The development and initial validation of a questionnaire on smoking urges. *Br. J. Addiction* **6**:1467–1476 (1991).
5. K. O. Fagerstrom. Measuring degree of physical dependence to tobacco smoking with reference to individualization of treatment. *Addict. Behav.* **3**:235–241 (1978).
6. W. J. Jusko and H. C. Ko. Physiologic indirect response models characterize diverse types of pharmacodynamic effects. *Clin. Pharmacol. Ther.* **56**:406–419 (1994).
7. J.-M. Gries, N. Benowitz, and D. Verotta. Chronopharmacokinetics of nicotine. *Clin. Pharmacol. Ther.* **60**:385–395 (1996).
8. N. L. Dayneka, V. Garg, and W. J. Jusko. Comparison of four basic models of indirect pharmacodynamic responses. *J. Pharmacokin. Biopharm.* **21**:457–478 (1993).
9. S. L. Beal, L. B. Sheiner. *NONMEM User's Guide,* University of California at San Francisco, San Francisco, CA, 1992.
10. H. Bozdogan. Model selection and Akaike's information criterion (AIC): The general theory and its analytical extensions. *Psychometrika* **52**:345–370 (1987).
11. K. J. Schuh and M. L. Stitzer. Desire to smoke during spaced smoking intervals. *Psychopharmacology* (*Berlin*) **120**:289–295 (1995).
12. N. G. Sneider, M. E. Jarvik, and A. B. Forsythe. Nicotine vs. placebo gum in alleviation of withdrawal during smoking cessation. *Addict. Behav.* **9**:149–156 (1984).
13. M. E. Jarvik, D. C. Masden, R. E. Olmstead, P. N. Iwamoto-Schaap, J. L. Elins, and N. L. Benowitz. Nicotine blood levels and subjective craving for cigarettes. *Pharmacol. Biochem. Behav.* **66**:553–558 (2000).
14. J. V. S. Gobburu and W. J. Jusko. Role of dosage regimen in controlling indirect pharmacodynamic responses. *Adv. Drug Deliv. Rev.* **33**:221–233 (1998).