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Pharmacodynamic Model of Tolerance: Application to Nicotine[1]

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ABSTRACT

The authors propose a model of pharmacodynamic response that, when integrated with a pharmacokinetic model, allows characterization of the development of functional tolerance. The model may be conceived of in several equivalent ways; one of these sees tolerance as a result of (noncompetitive) antagonism of agonist effect by a hypothetical substance (*e.g.*, metabolite) produced by a first-order process, driven by agonist concentration. Tolerance thus lags behind, and is approximately proportional to, agonist concentrations. Two new parameters quantifying tolerance are introduced: k_{ant0}, which describes the elimination kinetics of the antagonist and determines the rate of development and disappearance of tolerance, and $C_{ant_{50}}$, which determines the magnitude of tolerance that can be achieved. The model was tested in eight volunteers on data produced after three sequences of paired i.v. administrations of nicotine separated by different intervals of time. Blood concentrations of nicotine and heart rate were measured. The proposed tolerance model was fitted to the nicotine data. The estimate of k_{ant0} suggests a half-life of development and regression of tolerance of 35 min, and the estimate of $C_{ant_{50}}$ suggests that tolerance, at its full development, causes an approximately 80% reduction of initial (nontolerant) effect. This model provides a quantitative pharmacokinetic-pharmacodynamic description of the development of acute tolerance that also carries physiologic meaning. The quantitative information provided by this model may improve understanding of the temporal patterns of drug abuse and complications thereof.

The phenomenon of decreased effect with prolonged exposure to a drug is called tolerance. When it occurs within the time course of a single dose, it is called acute tolerance or tachyphylaxis. Acute tolerance may be related to change in the numbers of receptors in the target tissue, depletion of a second endogenous intermediary such as catecholamines and/or a physiologic adjustment by counterregulatory systems (Haefely, 1986; Kalant *et al.*, 1971; Sibley and Lefkowitz, 1985). Although much experimental work on tolerance has been performed, little has been published on the quantitative aspects of tolerance (Chow *et al.*, 1985; Hammarlund *et al.*, 1985; Licko and Raff, 1985; and Zahler *et al.*, 1982). Quantitative information on rate and extent of development of tolerance might suggest directions for mechanistic investigations and provide a description of the pharmacodynamic properties of particular drugs to which tolerance develops. This description could be used to choose drug regimens minimizing the development of tolerance. Because many drugs of abuse are subject to development of tolerance, quantitative information on this might improve our understanding of the specific temporal patterns of drug abuse and related complications.

We present an integrated pharmacokinetic-pharmacodynamic model that allows the description of the development of acute tolerance to the effect of a drug. Nicotine was chosen as test substance because previous studies have demonstrated acute tolerance to its cardioaccelerating effects (Benowitz *et al.*, 1982; Rosenberg *et al.*, 1980). We have reported previously that, with a single i.v. infusion of nicotine, one cannot distinguish true acute development of tolerance from apparent tolerance due to distribution kinetics (Porchet *et al.*, 1988). Accordingly, in the present study nicotine was administered by successive infusions separated by different intervals of time to allow the observation of development and disappearance of tolerance.

Methods

Subjects. The subjects were eight healthy men, 22 to 43 years old (mean: 36), who were habitual cigarette smokers. They smoked an average of 36 cigarettes per day (range: 20–50) with an average yield of 1.06 mg of nicotine (range: 0.9–1.3) and 17.1 mg of tar (range: 14–23) per cigarette based on United States Federal Trade Commission smok-

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ABBREVIATION: bpm, beats per minute.

ing machine delivery data. Biochemical tests of liver function (serum glutamic-oxaloacetic transaminase, lactic dehydrogenase, alkaline phosphatase, total protein and albumin) and kidney function (blood urea nitrogen, serum creatinine) were all within normal limits.

Experimental protocol. The subjects were hospitalized for four consecutive days on the clinical research ward of the San Francisco General Hospital. They ate a normal diet except that both caffeine- and alcohol-containing beverages were excluded. On the mornings of the 2nd, 3rd and 4th days, after an overnight fast and abstinence from smoking, two identical infusions of nicotine were administered. The two infusions were separated, on different days, by different time intervals. At least 1 hr before the first infusion was started, i.v. catheters were inserted into an antecubital vein of one arm for injection of nicotine and into a forearm vein of the other arm for blood sampling. During the experiment, subjects remained in the recumbent position, except to void. Heart rate was recorded by electrocardiogram (Grass model 7 polygraph) for 20 min before (minimum of five recordings) to obtain base-line values, and at frequent intervals during infusion of nicotine.

Nicotine bitartrate in sterile 0.9% sodium chloride was infused at a constant rate by infusion pump. On each of the 3 days, subjects received two infusions of 2.5 μg of nicotine base per kg per min for 30 min. On 1 day (treatment A), the second 30-min infusion was begun 60 min after the end of the first 30-min infusion, on another day (treatment B) 120 min and another day (treatment C) 210 min. The order of the treatment days was balanced across subjects. Blood samples for measurement of concentrations of nicotine were drawn at frequent intervals from time 0 to 380 min. Heart rate was recorded just before a blood sample was taken.

Nicotine analysis. Blood samples were assayed for concentrations of nicotine by gas chromatography using nitrogen-phosphorus detection, modified for use with capillary columns (Jacob *et al.*, 1981).

Pharmacokinetic-pharmacodynamic model. The model developed to describe tolerance is easiest to appreciate when presented as a compartmental model involving (real and hypothetical) drug concentrations (fig. 1). The model consists of several parts. The first is a classical pharmacokinetic model with two compartments to describe the pharmacokinetics of nicotine. Linked to the pharmacokinetic model is a pharmacodynamic model that relates the observed concentration of nicotine in the central pharmacokinetic compartment, C, to the observed effect, E. The model could have located the effect site in a separate "effect" compartment (Sheiner *et al.*, 1979), linking E to the concentration there rather than to C. This would account for distributional disequilibrium between C and E. All of the subsequent development would still apply but would be more complicated. We chose the simpler approach described here because our experiments were planned to involve only slow infusions of drug, thereby assuring that distributional disequilibrium, if present at all, would be negligible.

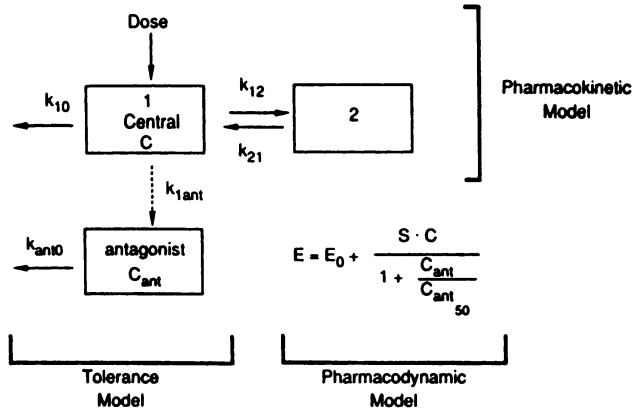

Fig. 1. Diagrammatic representation of the pharmacokinetic and pharmacodynamic model proposed for nicotine tolerance. The k_{ij} are the intercompartmental and elimination rate constants, C is the concentration of the agonist, C_{ant} is the concentration of the hypothetical antagonist, S is the slope of the linear relationship between effect and concentration, E is the effect, and E_0 is the base-line effect.

The pharmacodynamic model is modified by postulating the generation of a hypothetical substance (*e.g.*, a "metabolite" of nicotine) that acts as a noncompetitive antagonist of the effects of nicotine. The hypothetical antagonist is assumed to arise by a first-order process, driven by the concentration of nicotine in the central compartment. Because the antagonist is hypothetical, no mass balance restrictions need apply. To define a suitable scale for antagonist "concentrations," the model postulates that the steady-state concentration of the antagonist, $C_{ant_{SS}}$, is equal to the steady-state concentration of nicotine in the central compartment, C_{SS}. The model further assumes first-order loss of antagonist (tolerance) at a rate k_{ant0}. The parameter, k_{ant0}, thus determines the rate of appearance and disappearance of tolerance. The ratio of V_{ant}, the hypothetical volume of distribution of the antagonist, to k_{ant}, the rate of generation of the antagonist, is fixed so that the aforementioned steady-state condition is fulfilled: $V_{ant}/k_{1ant} = V_c/k_{ant0}$, where V_c is the volume of distribution of the central compartment of nicotine. Because of these choices, C_{ant} has units of steady-state nicotine concentration. The parameter $C_{ant_{50}}$ quantifies the degree of tolerance attainable for a given steady-stage nicotine concentration. A reasonable model for the effects of nicotine plus the hypothetical noncompetitive antagonist is (Ariens and Simonis, 1964)

$$E = E_O + \frac{E_{max}(C/C_{50})}{(1 + C_{ant}/C_{ant_{50}})(1 + C/C_{50})}, \quad (1)$$

where E_O is the base-line effect, E_{max} is the maximal effect and C_{50} is the concentration of nicotine that would produce half the maximal effect if there were no tolerance.

As stated, the first-order process creating C_{ant} is driven by C. Hence, C_{ant} and C cannot be adjusted independently. This may cause the model to be unidentifiable. Thus, in the presence of tolerance, one may not be able to estimate E_{max} because a response that stops increasing despite the continuing increase of C may be due either to development of tolerance or to having reached the maximal response portion of the dose-response curve. Assuming a linear model for effect in the absence of tolerance (equivalent to assuming that nicotine concentrations are always much smaller than C_{50}) allows equation (1) to be simplified to the identifiable form:

$$E = E_O + \frac{S\,C}{(1 + C_{ant}/C_{ant_{50}})}, \quad (2)$$

where S is equal to the ratio E_{max}/C_{50} of equation (1) and here is the slope of the linear relationship between concentration of nicotine and effect.

There is no known antagonistic substance produced by nicotine. The model has been presented in this way only for clarity. The model can also be conceptualized with C_{ant} not as a real substance but as a "force" driving tolerance. As such, it quantifies empirically the time course of tolerance and its relationship to exposure to the drug (agonist). As defined by our model, C_{ant} at any time t is proportional to the convolution integral:

$$\int_0^t C(\tau)e^{-k_{ant}(t-\tau)}d\tau.$$

Thus, the "force" driving tolerance is directly proportional to the intensities of past exposures to the antagonist, $(C(\tau))$, but each intensity is (exponentially) decremented with increasing time, $(t - \tau)$, since exposure to it. The rate constant quantifying the time-dependent decrement in tolerance in the absence of further exposure is, then, k_{ant0}.

Equation (2) shows how the "force" driving tolerance, (C_{ant}), acts to reduce drug effect (which varies between 0 and E_{max}). Equation (2) is derived from a noncompetitive antagonist receptor model to stress that the "force" driving tolerance is consistent with the process of receptor down-regulation, which corresponds to a noncompetitive antagonism mechanism, but the same equation can be derived assuming competitive antagonism.

Data analysis. A biexponential equation describing the two-compartment mammillary model was fitted to the mean blood nicotine concentrations of the eight subjects using extended-least-squares nonlinear regression (Peck *et al.*, 1984). The resulting pharmacokinetic parameter estimates were then used to fit the pharmacodynamic model to the corresponding mean effect data, also using extended-least-squares nonlinear regression.

Results

Nicotine infusions were well tolerated by all subjects. The left-handed sides of figures 2 through 4 show the mean blood concentration *vs.* time curves for treatments A, B, and C, respectively. The first 110 min of the curves for all three treatments are almost superimposable. All reach a maximum concentration of approximately 30 ng/ml of nicotine at the end of the first infusion (30.8 ± 11.5, 29.5 ± 10.2 and 29.8 ± 9.7 ng/ml, mean ± S.D. of group, for treatments A, B and C, respectively). With the second infusion, the maximum nicotine concentrations were 46, 38 and 39 ng/ml when given 1, 2 and 3.5 hr, respectively, after the end of the first infusion.

The right-hand sides of figures 2 through 4 show the corresponding values of the mean heart rate plotted against time. Maximum heart rates, at the end of the first infusion, are similar (76.9 ± 9.2, 78.1 ± 8.2 and 76.8 ± 9.7 bpm, mean ± S.D. of group, for treatments A, B and C, respectively). In contrast to the nicotine concentration curves, the maximum heart rate is smaller (72.9 bpm) when the second infusion is given 1 hr after the first one. Thus, the smallest maximum response after the second infusion is achieved with the highest peak blood concentration of nicotine. As the time interval between the two infusions increases, the amplitude of the response to the second one increases and is completely restored to the first infusion level (80.0 bpm) when the second is given 3.5 hr after the end of the first. These findings indicate rapid appearance and disappearance of tolerance to the cardioaccelerating effect of nicotine. This is illustrated in figure 5, where the effect *vs.* concentration curves are depicted for each treatment. Each panel shows two clockwise hysteresis loops. The first loop, corresponding to the first infusion of nicotine, is of similar shape for all three treatments. The loop corresponding to the second infusion (dashed line) shows almost no hysteresis for treatments A and B. The "slope" of the second loop is attenuated relative to the first, especially for treatment A. In contrast, for treatment C, the second loop is almost superimposable upon the first, indicating that the same relationship exists between concentrations of nicotine and effect for both infusions.

Table 1 presents the pharmacokinetic and pharmacodynamic parameter estimates obtained from the fit of the tolerance model (see "Methods") to the mean data of the eight subjects. Lines of best fit for heart rate are presented in figures 2 through 4. The estimated value of k_{ant0}, 0.0195 min^{-1}, indicates that the half-life of tolerance development to nicotine is approximately 35 min. The estimated value of $C_{ant_{50}}$, 7.72 ng/ml, indicates that, with full development of tolerance at a steady-state concentration of 30 ng/ml of nicotine [corresponding to the average nicotine concentration found in regular smokers during the daytime (Benowitz *et al.*, 1984)], the effect induced will be reduced to approximately 20% of the effect that would have been present had no tolerance developed. Thus, because at steady state $C_{ant_{SS}}$ is equal to C_{SS}, the denominator of equation (2) becomes equal to

$$1 + \frac{30}{7.72} = 4.9.$$

This value divides S, the slope of the linear relationship between concentration of nicotine and effect, thus reducing the effect at any given C, relative to the nontolerant state, by about 80%.

The precision of the parameter estimates was acceptable in that all coefficients of variation were less than 20%. A relatively high degree of correlation ($r = -0.91$) was found between the estimates of S and $C_{ant_{50}}$, as expected from the previously mentioned unavoidable correlation between C and C_{ant}. No other significant correlations between parameter estimates were observed.

Discussion

Nicotine tolerance. Our experiment demonstrates rapid acute development of tolerance to the cardioaccelerating effect of nicotine. This is suggested by the presence of clockwise hysteresis when heart rate is plotted against the corresponding concentration of nicotine during the initial 30-min infusion. The presence of this hysteresis means that a smaller effect is obtained at a given concentration of nicotine later in time. However, as we have reported previously, the finding of clockwise hysteresis does not in itself prove that acute tolerance is present (Porchet *et al.*, 1988). Clockwise hysteresis can also be a consequence of the distribution characteristics of a drug. This occurs when the effect site, *e.g.*, the brain or heart, equilibrates

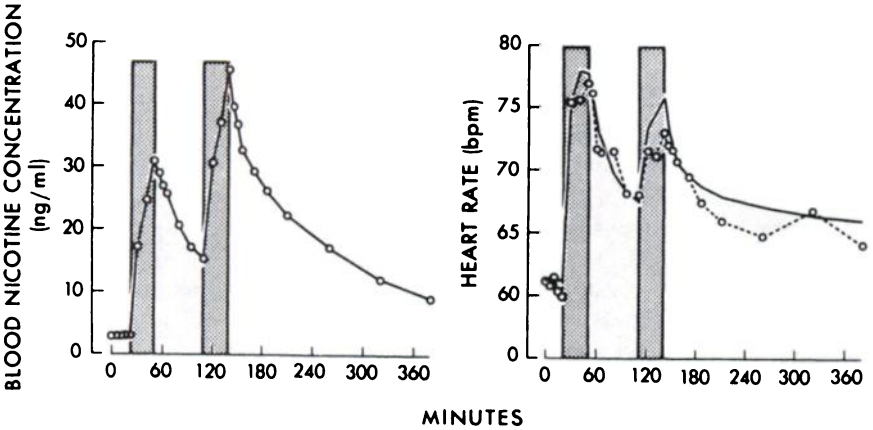

Fig. 2. Mean blood concentrations of nicotine (left panel) and the corresponding mean heart rate (right panel) in eight subjects after two 30-min i.v. infusions of 25 μg/kg/min of nicotine beginning 1 hr apart (treatment A; see text). The shadowed area indicates the periods during which nicotine was infused. The solid line in the right panel shows the fit of the model of figure 1 to the effect data.

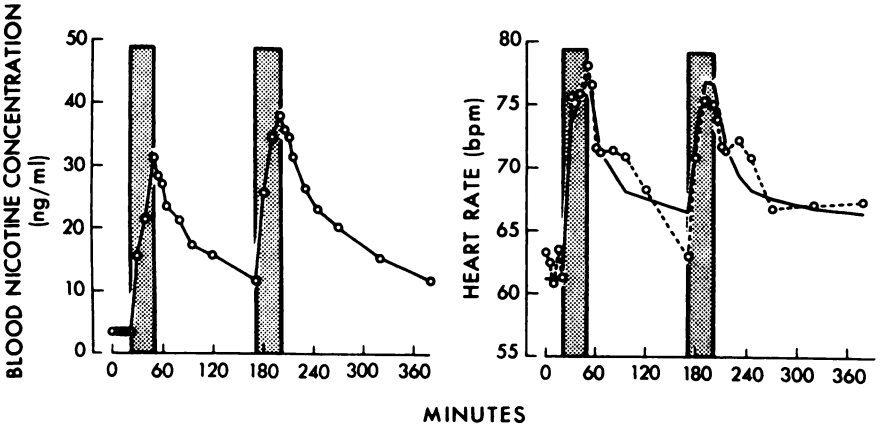

Fig. 3. The same as figure 2 for two 30-min infusions of nicotine as for treatment A, but beginning 2 hr apart (treatment B).

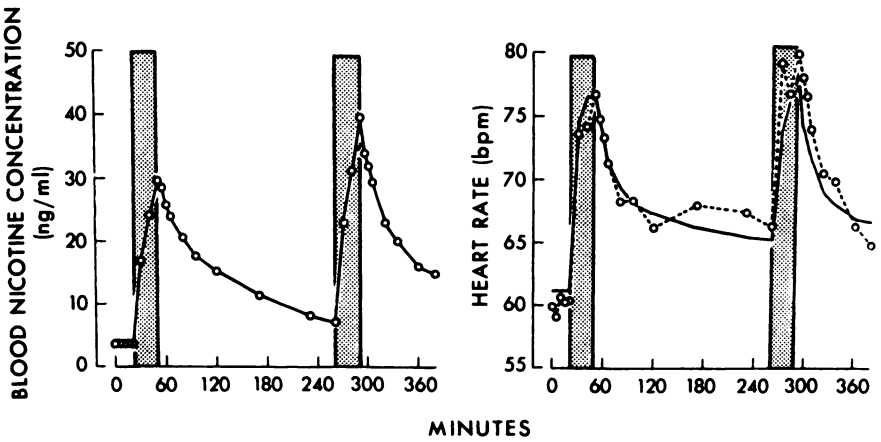

Fig. 4. The same as figure 2 for two 30-min infusions of nicotine as for treatment A, but beginning 3.5 hr apart (treatment C).

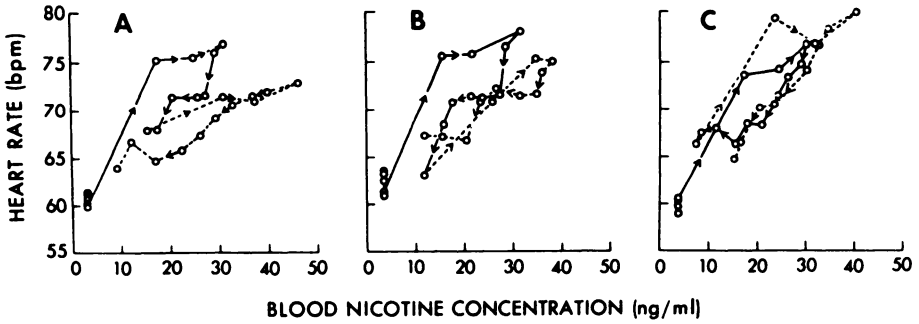

Fig. 5. Mean heart rate plotted against simultaneous mean blood concentrations of nicotine (hysteresis loops) for treatments A, B and C. The solid line correspond to the first infusions; the dashed lines correspond to the second infusions. Arrows indicate the progression of time during and after nicotine infusion.

TABLE 1

Pharmacokinetic and pharmacodynamic parameter estimates of tolerance model

Parameters Units	k_{10} min^{-1}	k_{12} min^{-1}	k_{21} min^{-1}	V_C liter	k_{em0} min^{-1}	S bpm/ng/ml	$C_{em_{50}}$ ng/ml	E_O bpm
Estimates[a]	0.0112	0.03	0.0325	114	0.0195	1.31	7.72	61.2
c.v. (%)[a]	5.2	15.0	9.2	5.1	13.8	12.8	18.8	0.5

[a] Parameter estimates are derived from the average data of all subjects; the c.v. describes estimation error, not interindividual variability.

with arterial drug concentrations faster than does the concentration at the sampling site, *e.g.*, forearm venous blood. However, distributional considerations cannot explain the results seen with the second infusion of nicotine in our experiments. If distribution kinetics were the only explanation for hysteresis, the greatest peak effect would be associated with the highest blood concentration of nicotine (at the end of the second infusion given with the shortest time interval after the end of the first one). This was not observed. That the smallest response follows the most closely paired infusion indicates that tolerance to the effects of nicotine has occurred. This does not exclude the possibility that some of the clockwise hysteresis we observe is a consequence of nicotine distribution kinetics, but, because we used a relatively slow rate of nicotine infusion, the role of distribution kinetics is probably not large. We find that the rate of appearance-disappearance of tolerance is rapid; approximately 3 hr after the end of the one exposure, tolerance has completely disappeared.

Rosenberg *et al.* (1980) have shown, in a previous study, that, when short (10-min) i.v. infusions of nicotine are given every

30 min, the intensity of the response (increase in heart rate) induced by the first infusion is much greater than that induced by the following infusions, despite observing that, with each successive infusion, higher blood concentrations of nicotine are achieved. Earlier, Russell and Feyerabend (1978) showed that the increase in heart rate after a rapid i.v. injection of nicotine is much smaller when the injection is administered after the subjects have smoked several cigarettes than after overnight abstinence from nicotine (Russell and Feyerabend, 1978). Here, too, higher nicotine concentrations were observed with the dose inducing the smaller response. These results are in agreement with our findings and confirm that acute tolerance develops to the cardioaccelerating effect of nicotine.

Due to individual variability in heart rate and to difficulties in fitting a two-compartment kinetic model to blood level data of some subjects, data analysis was done on the average values of all eight subjects. This results in smoothing of the curves and facilitates the fitting procedure. It should be noted, however, that the same response pattern seen with the average values was observed in the values of each individual; the lowest peak effect was observed with the highest peak concentration of nicotine obtained after the second infusion of treatment A, and nearly complete restoration of nicotine effects was seen with the second infusion of treatment C.

Tolerance model. As discussed in "Methods", our tolerance model postulates a "force" driving tolerance, that acts as a noncompetitive antagonist and that is greater the greater the intensity of past exposure to agonist and is less the more remotely in time that exposure occurs. There is but a single rate constant, k_{anto}, governing the waxing and waning of tolerance in response to exposure to agonist. Accordingly, if agonist concentration were suddenly to rise and to stay at a fixed value, the rate of appearance of tolerance would be the same as its rate of disappearance if agonist concentrations were to drop suddenly from a previously sustained fixed value to zero.

As shown in figure 2, our model fits the nicotine data relatively well. However, the effect of the second peak of treatment A is slightly overestimated, and that of treatment C is slightly underestimated. This suggests that the rates of development and disappearance of tolerance are not the same but that tolerance disappears more quickly than it appears. Another possible explanation of this relative lack of fit is that the baseline heart rate increased during the experiment.

To our knowledge, four other models have been proposed to describe the pharmacodynamics of tolerance. One of them uses an integrated pharmacokinetic-pharmacodynamic approach to model the effects of cocaine on heart rate (Chow *et al.*, 1985). These authors model the reciprocal of our "force" driving tolerance as a function (G) that starts at unity and declines exponentially as a function of time only (independent of past intensity of exposure to agonist). Instead of equation (2), their (reciprocal) "force" driving tolerance, G, acts on drug effect by multiplying the slope, S, of a postulated linear relationship (like ours) of cocaine concentration to effect. This model implies that, if a steady-state concentration of cocaine is maintained long enough, drug effect will eventually disappear entirely. Because this model ignores agonist kinetics per se and assumes monotonically increasing tolerance, the model can, at best, describe only experiments in which tolerance is expected to increase throughout—*i.e.*, experiments with high and sustained agonist concentrations. This model does not allow for the influence of different doses or levels of exposure to agonist on development of tolerance and does not allow tolerance to decrease at some later time when agonist has disappeared. Such a model could not describe the results of our experiments, involving, as they do, two sequential peaks of agonist.

Hammarlund *et al.* (1985) describe a model for the acute development of tolerance to furosemide-induced diuresis based on a similar assumption. They modify the classic E_{max} model by allowing the parameter C_{50} (representing the sensitivity of the system) to decrease exponentially as a function of the cumulative excretion of furosemide. The same criticisms as above apply to this model, except that this model does not necessarily imply full tolerance.

A third model for tolerance uses a time-series-type model (Zahler *et al.*, 1982). This model is excessively empirical although it can be expected to respond to the kinetics of the agonist.

A semimechanistic model for tolerance with an appealing physiologic interpretation has recently been put forward (Ekblad and Licko, 1984). The model proposes the transformation of a hypothetical substance X (which could be conceptualized as receptors) to a substance Y (which could be conceptualized as occupied receptors), the rate of which is influenced by the concentration of the agonist. This model assumes that the substance X is produced at a constant rate [(re-)generation of available receptors] and that it is eliminated at a first-order rate (degradation of receptors). The substance Y is eliminated at another first-order rate (down-regulation of receptors). If the pharmacologic effect is related to the amount of Y, the system will respond transiently to an alteration of the concentration of the agonist. When this model is fit to our data, the fit is significantly less good than the fit obtained with our model. Nonetheless, it remains an attractive alternative.

Significance of the model as applied to nicotine. As discussed earlier, our model is empirical although it can be interpreted as a model of receptor down-regulation. For nicotine, the idea of receptor down-regulation may seem inappropriate because studies conducted *in vivo* in rats and mice have shown that the number of nicotine receptors in the brain increases after chronic administration of nicotine and induction of tolerance (Marks *et al.*, 1983; Schwartz and Kellar, 1983). Further studies have shown that changes in receptor binding are correlated with the acquisition and loss of tolerance (Marks *et al.*, 1985). These authors suggested three possible explanations of the increase in receptor numbers: 1) nicotine or a metabolite is acting directly as an antagonist, 2) nicotine acts indirectly by reducing the availability of acethylcholine for release or 3) nicotine desensitizes or inactivates its receptors during chronic treatment, functionally acting as an antagonist. The net result of each of these three mechanisms is an increase in the total numbers of receptors but a decrease in the number of receptors that are functional. This is functionally equivalent to down-regulation of active receptors, and the kinetics of tolerance by this mechanism could be described by the model we propose. A major difference between the cited studies in animals and our studies in humans is that the development of tolerance in animals takes days whereas in humans it takes minutes. Because the subjects we investigated are chronic cigarette smokers, it is possible that long-term tolerance equivalent to that observed in animals has already developed and that we are dealing with another aspect of tolerance.

The pharmacokinetic model estimates the pharmacokinetic parameters of nicotine (table 1). The total clearance calculated

as $k_{10} \times V_c$ is 1.27 liters/min, and the volume of distribution at steady state ($V_c \times (1 + k_{12}/k_{21})$) is 219 liters. The half-life of the α-phase is 10 min, and that of the β-phase is 124 min. All these parameter estimates are in good agreement with previous data published on nicotine kinetics using a noncompartmental analysis (Benowitz *et al.*, 1982; Feyerabend *et al.*, 1985). Thus, the two-compartment mammillary model used to describe nicotine kinetics is adequate.

Our model of nicotine tolerance fits the data best with a half-life of development and regression of tolerance of 35 min. This indicates that, four to five half-lives (about 3 hr) after a cigarette, nearly full sensitivity should have been regained. The interval at which smokers smoke cigarettes may be determined by the kinetics of regression of tolerance. Our results indicate that tolerance to the cardioaccelerating effect of nicotine is not complete. As indicated by the estimate of $C_{ant_{50}}$ (7.72 ng/ml), approximately one fifth of the effect that would have been present had tolerance not developed should persist at expected steady-state levels of nicotine in smokers. This finding is in agreement with a previous study showing that, when smokers smoke *ad libitum*, the increase of heart rate above first morning values is greater in the first few hours in the morning (when tolerance is, presumably, not fully developed) than it is later in the day. After this the heart rate follows a circadian pattern similar to (but at a faster rate than) that seen during abstinence from smoking (Benowitz *et al.*, 1984).

Our model for nicotine tolerance may help to elucidate certain aspects of smoking behavior. The daily smoking cycle can be conceived as follows. The first cigarette of the day produces substantial pharmacologic effects, primarily arousal, but at the same time tolerance begins to develop. A second cigarette may then be smoked after some regression of tolerance. With subsequent cigarettes, there is accumulation of nicotine in the body, resulting in sustained tolerance. The effect of individual cigarettes tends to lessen throughout the day. Overnight abstinence allows considerable resensitization to the action of nicotine. However, full resensitization requires a longer time because some nicotine still persists in the body. Because of dose-response and tolerance characteristics, the typical habitual smoker needs to smoke at least 15 cigarettes and consume 20 to 40 mg of nicotine to achieve desired effects of cigarette smoking throughout the day.

The rapid development of tolerance to nicotine suggests a possible basis for the relatively poor performance of nicotine gum in promoting smoking cessation (Jamrozik *et al.*, 1984). The successive peaks of high nicotine concentration, as obtained by cigarette smoking, are better able to overcome tolerance partially to produce psychologic effects. Further, the decline of nicotine levels between cigarettes permits substantial regression of tolerance. In contrast, the slow rise in nicotine concentrations with use of nicotine gum and the more stable levels of nicotine concentration achieved may result in the full development of tolerance and its maintenance throughout the day with repeated gum administration. This type of dosing minimizes drug effects and may explain why the gum is not perceived as very satisfying.

In summary, we present a model that simultaneously describes the pharmacokinetics and pharmacodynamics of drugs inducing tolerance. The model, as it is presented, does not distinguish distributional phenomena from true tolerance. However, such a distinction is not needed because our study design (slow infusion rate) minimizes distributional disequilibrium. The model can be expanded to deal with these issues if they are present. Our model has advantages compared with previously published models. It allows a complete quantitative description of tolerance and is able to define the following pharmacodynamic characteristics: 1) the (naive) sensitivity of the system, S, 2) the time constant for development and regression of tolerance, k_{ant0}, 3) the steady-state extent of tolerance development as a function of the intensity and duration of drug exposure, $C_{ant_{50}}$. Although we have studied the application of our model only to nicotine, we believe that this model may be applicable to other drugs known to induce tolerance. Such a quantitative description of tolerance may be helpful in designing specific drug regimens that minimize development of tolerance and maximize therapeutic efficacy.

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