Variability in Human Drug Response
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Tolerance as a Modulator of Drug Response

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ABSTRACT

Development of tolerance to the effects of drugs is a common phenomenon in medicine. The development of tolerance has implications with respect to therapeutic outcomes and in planning medication regimens. This paper will focus on the development of tolerance to psychoactive and cardiovascular drugs, with an emphasis on methods for studying drug tolerance in humans.

Several pharmacokinetic-pharmacodynamic models have been proposed for studying drug tolerance. In various models tolerance is driven by time, drug concentration, or by the effect itself. The latter type of physiological model allows modelling of both tolerance and withdrawal effects.

Tolerance to different pharmacologic actions of a drug may develop at different rates and/or to different extents. Differences in the development of tolerance to different effects of a drug may provide insight into mechanisms of drug action and have implications for drug safety.

Key words: tolerance, pharmacodynamics, pharmacokinetics, modelling, nicotine, toxicity.

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INTRODUCTION

The development of tolerance to effects of drugs is a common phenomenon in medicine. Tolerance develops to the actions of a variety of drugs, including psychoactive drugs,

analgesics, and cardiovascular drugs. The development of tolerance has important implications with respect to therapeutic outcomes and for planning medication regimens. This paper will focus on the development of tolerance to psychoactive and cardiovascular drug effects, with an emphasis on methods for studying the development of tolerance in humans.

WHAT IS TOLERANCE?

A broad definition of tolerance is "a pharmacologically defined phenomenon that appears after one or several exposures to a drug, when the same dose or concentration of the same drug produces a smaller response than that which appears in appropriate controls" [1].

It is useful to consider examples of ways of measuring tolerance. 1) Decreased duration of a drug effect — for example, a progressive decrease in the duration of analgesia with repeated doses of narcotics. 2) Reduced intensity of response to a particular dose — for example, a reduced hypnotic effect of a sleeping pill taken on a regular basis. 3) Increased dose required to produce a given effect — for example, increased doses of nitroglycerin needed to vasodilate and control symptoms of angina pectoris. 4) Significant hysteresis in the plasma concentration time curve. The latter has been used in modeling short term tolerance to the acute effects of drugs [2].

WHY IS TOLERANCE IMPORTANT?

The development of tolerance may be important in a variety of ways. 1) The most obvious is that tolerance reduces the therapeutic effect of a drug given repeatedly over time. This is well illustrated by the development of tolerance to the anti-ischemic effects of transdermal nitroglycerin given to patients with angina pectoris, and to the effects of opiates given in chronic pain patients. 2) A second implication of toxicity is less toxicity after chronic exposure. An example of toxicity reducing tolerance is less sedation or respiratory depression with chronic opioid use. 3) The development of tolerance is also associated with the development of physical dependence, which is seen with a variety of substances of abuse. Physical dependence refers to the development of withdrawal symptoms when a drug is stopped after a period of drug administration. The same mechanism involved in the development of tolerance is often involved in producing withdrawal symptoms. Physical dependence is one element, although not a required element, in the development of addiction. Many psychoactive drugs are associated with the development of tolerance and physical dependence, including caffeine, nicotine, alcohol, heroin, and sedative hypnotics.

MECHANISMS OF DEVELOPMENT OF TOLERANCE

The general mechanisms of tolerance can be considered in several general categories including 1) dispositional or pharmacokinetic tolerance; 2) functional or pharmacodynamic tolerance; 3) behavioral tolerance, and 4) conditioned tolerance. Dispositional tolerance occurs when repeated doses of a drug results in accelerated metabolism. An example of this is with repeated administration of barbiturates or ethanol [3]. Dispositional tolerance is not a common

mechanism of tolerance and can explain only moderate tolerance — that is, reducing the tolerant response to only two to three times compared to the initial response.

Functional or pharmacodynamic tolerance implies that there is a different response in the presence of the same concentration of drug at the receptor site or other site of action. There are several ways in which pharmacodynamic tolerance can develop, as discussed below. Behavioral tolerance is a particular type of tolerance seen with psychoactive drugs. In this case, when an organism is exposed to a drug in the context of some behavior, that behavior can be learned in the presence of the drug with improvement over time. Thus, the individual learns to compensate for a particular drug effect. An example of this is the effects of marijuana smoking while driving an automobile. Driving can be learned when repeatedly performed under the influence of marijuana, but this tolerance does not necessarily extend to the effects of marijuana in other behavioral situations. Conditioned tolerance refers to the development of tolerance to a drug effect in a particular environment, while exposure to the same drug in another environment may not be associated with tolerance. This is purported to occur with the abuse of drugs such as alcohol or heroin. After development of tolerance to these drugs in a particular environment, exposure to a placebo in the same environment will produce an effect apparently opposite to that of the drug action. That is, the cues of drug taking elicit a compensatory or adaptive counterregulatory response.

Functional tolerance implies that there is a change in response with a particular concentration of a drug present at the receptor site. A variety of types of functional tolerance have been described. 1) Depletion of an endogenous intermediary. An example is a drug that releases catecholamines from neuronal stores, such as amphetamine. In this case, the repeated dosing of amphetamine results in a diminished cardiovascular response related to a reduction of intraneuronal catecholamine stores. 2) Inactivation or reduction in numbers of receptors. Changes in receptor function and structure are associated with the development of tolerance to beta adrenergic agonists, as well as other drugs. Initial rapid tolerance development (also termed desensitization) is associated with phosphorylation of receptors and sequestration of receptors in a cellular compartment no longer accessible to the agonist. Subsequently, uncoupling of the receptor from the second messenger system and, finally, internalization of the receptor to intracellular sites occurs [4]. Thus, agonists no longer have access to the receptors and tolerance is apparent. Receptor binding studies show the presence of fewer receptors. An interesting exception to the phenomenon of the apparent downregulation of receptors with the development of tolerance is seen with nicotine [5]. Chronic exposure to nicotine is associated with increased numbers of nicotinic binding sites. In this case, nicotine, while initially activating receptors, subsequently desensitizes receptors, functionally acting as an antagonist. The response to receptor antagonism is upregulation of receptors. 3) A third category of functional tolerance is the development of homeostatic feedback responses, as described below.

Homeostatic feedback is a well described mechanism of the development of tolerance to cardiovascular drugs. For example, with continuous infusion of sodium nitroprusside (or a number of other vasodilator drugs), tolerance develops to vasodilatory and hypotensive effects owing to the retention of sodium with the expansion of plasma volume, as well as sympathetic neural activation resulting in increased heart rate, myocardial contractility, cardiac output, and vasoconstriction [6]. The resultant increase in cardiac output and vascular resistance counteracts the hypotensive effects of the vasodilator. Understanding this mechanism of tolerance is important because other drugs can be used to prevent the development of

tolerance. For example, diuretics can prevent volume expansion and sympathetic blocking drugs can prevent the effects of endogenous sympathetic activation.

NICOTINE AS A MODEL DRUG TO STUDY TOLERANCE

The pharmacology of nicotine is of interest because nicotine mediates tobacco use, a major cause of premature death and disability. Nicotine is also being developed as a medication, both to aid smoking cessation and potentially for the treatment of other diseases, such as ulcerative colitis [7].

Tolerance is well known to develop to the noxious actions of nicotine that are experienced when a person smokes their first cigarette, but rapidly dissipates or disappears if smoking continues. The development of tolerance is associated with the development of physical dependence to nicotine and, as such, contributes to addiction. Rapid development of tolerance explains in part why delivery by routes such as smoking, that result in rapid absorption, are maximally reinforcing because the high resultant arterial concentrations can overcome tolerance [8]. Finally, tolerance is a key safety issue in considering the use of nicotine medications in aiding smoking cessation as well as in the development of nicotine for use in harm reduction, both situations in which smokers may continue to smoke cigarettes while receiving nicotine medications.

A brief review of the clinical pharmacology of nicotine is necessary to understand the studies of tolerance described later. Nicotine acts on nicotinic cholinergic receptors located in the brain, in autonomic ganglia, in the adrenal, and at the neuromuscular junction [7]. Nicotine acts, at least in part, presynaptically, such that nicotinic cholinergic activation augments the release of various neurotransmitters in the brain, including dopamine, norepinephrine, epinephrine, serotonin, and acetylcholine. Release of various neurotransmitters is thought to modulate the psychological effects of nicotine. Nicotine also produces generalized sympathetic neural activation, increasing circulating catecholamine levels, increasing heart rate and blood pressure, increasing metabolic rate, and stimulating lipolysis.

Animal and human studies have demonstrated substantial development of tolerance to various effects of nicotine. In animals, the development of tolerance has been associated with increased numbers of nicotinic cholinergic binding sites, as mentioned previously [5]. Two types of tolerance — acute and chronic tolerance — develop to the actions of nicotine. Within seconds of exposure to nicotine, acute tolerance develops related to conformational changes in the nicotine receptor [9]. Thus, the nicotine receptor appears to exist in both activatable and inactivatable states, with an equilibrium between the two, that is influenced acutely by exposure to nicotine. With prolonged nicotine exposure, the number of nicotine receptors increases, related primarily to a decreased rate of nicotine receptor catabolism [10]. While these receptors bind nicotine with normal affinity *in vitro*, *in vivo* these receptors are not as responsive to nicotine because of conformational changes, as discussed above.

PSEUDOTOLERANCE

A common method of examining tolerance is the use of plasma concentration-effect curves, also called hysteresis curves [2]. If a particular pharmacologic effect occurs at the

same blood concentration as levels of the drug increase and decrease, then a concentration-effect curve will be superimposable on the ascending and descending limbs of the concentration effect curve (Figure 1). If the effects are greater as blood levels are rising, and lower as concentrations are falling, the concentration-effect curve shows a different profile in the rising and falling phases producing a loop, also called hysteresis. Clockwise hysteresis has been interpreted as indicating the development of tolerance. Clockwise hysteresis has been observed for the venous plasma nicotine-heart rate accelerating effect curve during and after intravenous nicotine infusion [11]. Counterclockwise hysteresis may be interpreted as a lag between the appearance of nicotine in the blood stream and the observed effect. Counterclockwise hysteresis has been reported for the relationship between plasma procainamide concentration and electrocardiographic effect [12].

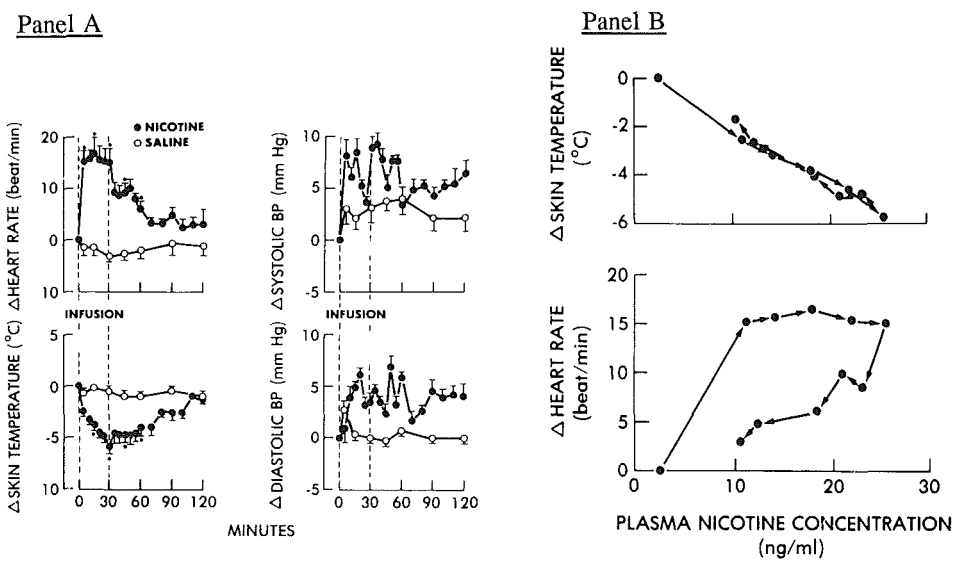

Figure 1. Example of plasma concentration-effect curves suggesting the development of tolerance or no tolerance. Panel A shows cardiovascular response to a 30 minute constant intravenous infusion of nicotine. Panel B top shows plasma venous nicotine concentration-skin temperature decline response (reflecting cutaneous vasoconstriction). There is no hysteresis seen, suggesting that the response is directly proportional to the venous plasma concentration. Panel B bottom shows the plasma venous nicotine concentration-heart rate acceleration curve. There is considerable hysteresis, suggesting that tolerance is developing during the course of drug exposure. Reprinted with permission from Benowitz *et al.* 1982 [11].

Clockwise hysteresis can also occur when the plasma concentration does not accurately reflect the concentration of drug at the receptor site, but rather the latter rises with a delay. This occurs when venous drug levels are used instead of arterial levels. With rapid dosing of

a drug, arterial levels are higher and peak earlier than do venous levels. Nicotine, as well as many other drugs, exhibits significant arterial venous differences after rapid dosing, such as after smoking a cigarette, but even after a 30 minute intravenous infusion [13]. When arterial levels rather than venous levels are used in constructing a plasma concentration effect curve, no apparent tolerance was seen (Figure 2). The misinterpretation of the relationship between venous concentrations and effect as tolerance, has been termed dispositional tolerance [14].

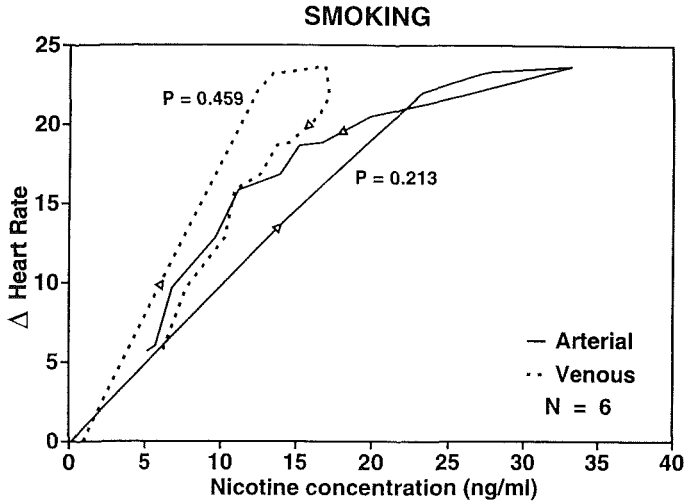

Figure 2. Illustration of dispositional tolerance. The figure shows mean arterial and venous heart rate response-concentration curves after smoking a cigarette. The dashed line representing venous plasma nicotine concentrations shows evidence of clockwise hysteresis, suggesting tolerance. However, the solid lines, indicating arterial plasma nicotine concentrations, show no evidence of hysteresis, indicating no evidence of tolerance. Reprinted with permission from Gourlay and Benowitz, 1997 [13].

EXPERIMENTAL PARADIGMS FOR STUDYING TOLERANCE

While it is difficult to define the extent of tolerance to the effects of a drug during the course of a single dose, owing to the problems of measuring arterial venous differences with rapid changes in drug levels, other dosing schemes can be used to assess tolerance. One approach is the use of repeated doses of a drug at varying intervals of time. When a second dose is administered in close temporal proximity to a previous dose, the extent of response will be lower due to the development of tolerance. If an adequate time is allowed between doses, tolerance will dissipate, resulting in a return of response of the challenge dose back to baseline. This approach has been used to examine the time course of development of tolerance to the effects of nicotine and caffeine (Figure 3) [15,16].

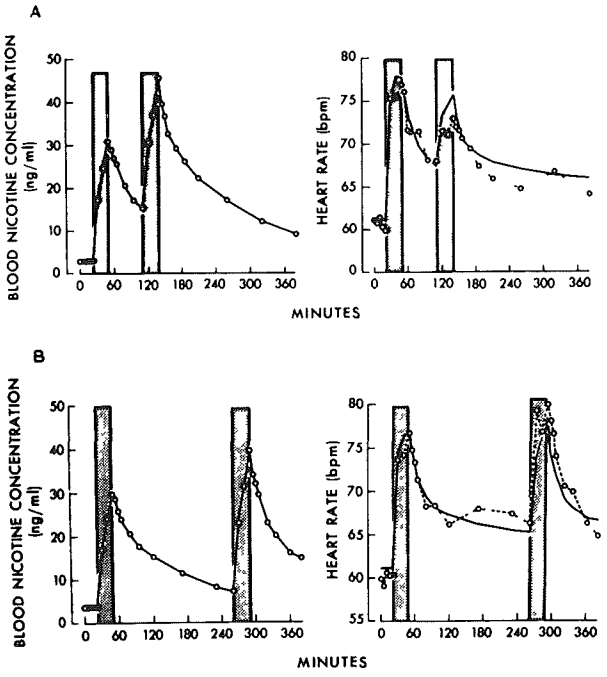

Figure 3. Mean blood concentrations of nicotine (Panel A) and the corresponding mean heart rate (Panel B) in eight subjects after two 30 minute intravenous infusions of nicotine separated by 60 minutes (A) or 210 minutes (B). The shadowed area indicates the period during which nicotine was infused. The solid line shows the fit of the model to the effect data. Reprinted with permission from Porchet *et al.*, 1988 [15].

Another approach is to infuse a drug to achieve and maintain a relatively constant plasma concentration over a prolonged period of time [17]. A decline of effects in a situation where blood concentrations are in steady state indicates the development of tolerance.

Both of these methods have been used to study the development of tolerance to the effects of nicotine, and have been used in constructing mathematical models for the pharmacodynamics of tolerance.

PHARMACOKINETIC-PHARMACODYNAMIC MODELS OF TOLERANCE

Several different types of pharmacokinetic-pharmacodynamic models have been proposed to characterize the pharmacodynamics of drug tolerance. All have the characteristics that the effects of the drug change over time. In the simplest model, the dependent variable is time (Figure 4). This model has been used to describe tolerance to heart rate acceleration following single doses of cocaine [18]. In this model, the drug effect declines over time, and this decline is determined by a mathematical construct called a "function generator". A limitation of this

model is that there is no way for the model to adapt to different drug doses or different drug dosing schedules, or from prior exposure to the drug.

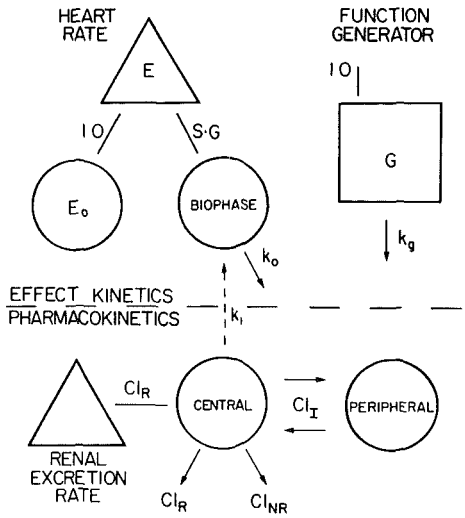

Figure 4. Pharmacokinetic-pharmacokinetic model used to model the development of tolerance to heart rate effects of cocaine. Tolerance is driven by time, via the function generator (G) that multiplicatively attenuates the function S that relates biophase cocaine concentration to effect. The function G has an initial value of 1.0 and an exponential decay rate, kg. E and E0 represent the observed and initial heart rate, respectively. The rate constants ki and k0 represent the relationship between cocaine concentration in the central compartment to that in the biophase compartment. Reprinted from Chow *et al.*, 1985 [18].

Another approach is where the drug concentration is the dependent variable that drives the development of tolerance. We have used such an approach in studying development of tolerance to the effects of nicotine and caffeine [15,16,17]. Others have used this type of model to study tolerance to morphine and furosemide [19,20]. In this case, the drug concentration drives tolerance either by postulating additive effect and tolerance functions, or by postulating the development of a response modifier equivalent to a competitive antagonist principle or metabolite (Figure 5). In the latter model, the hypothetical antagonistic metabolite is formed in proportion to the concentration of the drug in the central compartment, with elimination characterized by a particular rate constant that describes the rate of development and dissipation of tolerance. This type of model behaves such that the degree of tolerance increases as the concentration of the drug and the duration of the drug exposure increases. Such a model does not, however, predict withdrawal effects.

A third type of model is a more physiological model in which tolerance is driven by the effects of the drug. This type of model has been used to model tolerance to effects of

alfentanil and nitroglycerin [21,22]. In this case, tolerance is modeled as occurring through the development of homeostatic responses or as a change in cellular mechanism of drug response (for example, a sequestration of receptors, change in second messenger systems, etc.) (Figure 6). These more physiological models have the potential to predict complete or partial tolerance, can incorporate differences in baseline physiological states (related, for example, to different levels of endogenous substances acting on the receptor system of interest) and can incorporate different mechanisms of tolerance development.

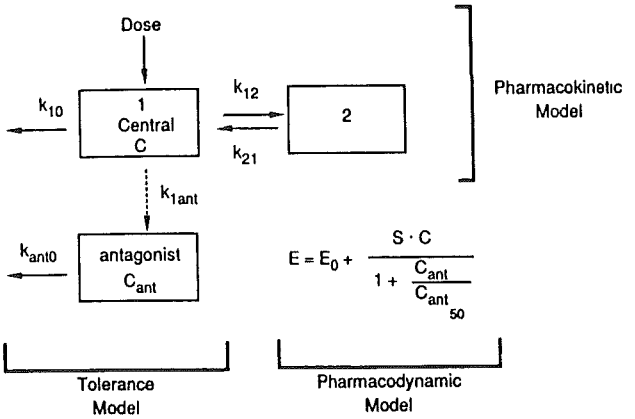

Figure 5. Inhibitory metabolite model of the pharmacokinetics and pharmacodynamics of nicotine tolerance. The k_{ij} are the intercompartmental and elimination rate constants, C is the concentration of the agonist, C_{ant} is the concentration of the hypothetical antagonist, S is the slope of the linear relationship between effect and concentration, E is the effect, and E0 is the baseline effect. Reprinted with permission from Porchet *et al.* [15].

STUDIES OF PHARMACODYNAMICS OF NICOTINE TOLERANCE

To illustrate the use of pharmacokinetic-pharmacodynamic models to study tolerance in humans, I will describe two studies from my laboratory on nicotine tolerance. The pharmacokinetic-pharmacodynamic model used is a drug concentration-driven "inhibitory metabolite" model, as previously described (Figure 4). In the first study, paired intravenous infusions of nicotine, separated by different intervals of time, were administered (Figure 3] [15]. Despite higher blood concentrations, heart rate acceleration and subjective effects were much less when a second infusion of nicotine was given at 60 or 120 minutes after the first infusion. With a 240 minute interval between infusions, however, the response was fully restored.

The pharmacodynamic parameters of most interest for characterizing tolerance are the half-life of development of tolerance and the concentration of drug at which 50% of the effect would have occurred compared to that which would have been seen without the development

of tolerance (Cm50). Our study revealed a half-life of development and regression of tolerance to heart rate acceleration of 35 minutes. We found a Cm50 of 7.7 ng/ml, which implies that at a steady state concentration of 30 ng/ml, a typical concentration for a cigarette smoker, the response to another dose of nicotine would be attenuated to 20% of that which would have been seen without the development of tolerance. Tolerance is predicted not to be complete, which is what has been found in observational studies [23].

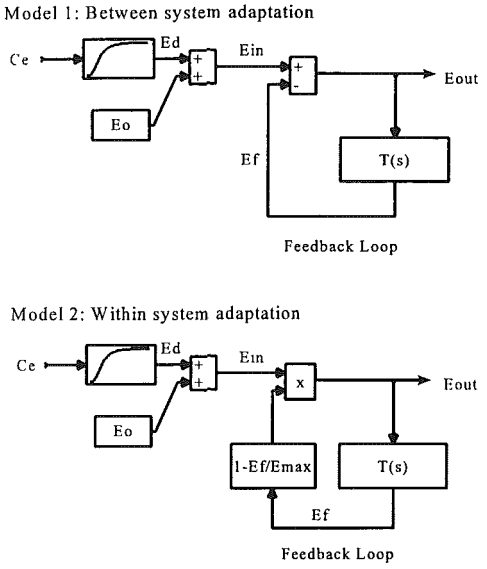

Figure 6. Tolerance models driven by pharmacologic effect. Model 1 illustrates between-system adaptation in which a pharmacologic effect elicits a compensatory or homeostatic effect that produces an action opposite to the initial drug effect, resulting in tolerance. Model 2 illustrates a within-system adaptation in which a pharmacologic effect triggers a regulatory response that changes one of the cellular components involved in producing the drug effect. Ce = effect site concentration; Ed = primary drug-induced effect; E0 = baseline effect caused by endogenous substances; Ein = sum of Ed and E0; Ef = opposing feedback response; T(s) = the transfer function that characterizes the regulatory mechanism; Emax = the maximum cellular regulatory response; Eout = net observed effect. Reprinted from Mandema and Wada, 1995 [21] .

A second study was performed using the same general pharmacokinetic-pharmacodynamic model. In this case, nicotine was infused rapidly to achieve a concentration of about 25 ng/ml, a level typical for smokers, followed by a computer controlled infusion to maintain this concentration for 180 minutes [17]. Tolerance to multiple nicotinic effects, including increases in heart rate, blood pressure, plasma epinephrine, and energy expenditure and free fatty acid concentrations were studied simultaneously. We found substantial differences in the rate and

extent of development of tolerance to various responses. For heart rate acceleration, the half-life of tolerance development (22 minutes) and the Cm50 (8.9 ng/ml) were similar to that described in the first study. Rates of development of tolerance and Cm50 values for blood pressure and plasma epinephrine were reasonably similar to those seen for heart rate, consistent with the idea that these are all sympathetic neural responses. The concordance suggests that epinephrine may contribute to these other hemodynamic responses. In contrast to the heart rate and epinephrine responses, the effect of nicotine on energy expenditure showed extremely rapid and essentially complete tolerance within 30 minutes. The half-life of development of tolerance was estimated to be 3.5 minutes.

Table 1.
Pharmacodynamic model of tolerance: parameter estimates

$$E = E_0 + \frac{SC}{(1 + C_{ant}/C_{ant_{50}})}$$

S = 1.31 bpm/ng per ml (12.8, C.V.%)

$C_{ant_{50}}$ = 7.72 ng/ml (18.8)

E_0 = 61.2 bpm (0.5)

K_{ant_0}) = 0.0195 · min^{-1} (13.8)

$t1/2_{tolerance}$ = 35 min

E	=	effect
E_0	=	baseline effect
S	=	slope of linear relationship between effect and concentration
C	=	concentration of nicotine
C_{ant}	=	concentration of the hypothetical antagonist
$C_{ant_{50}}$	=	concentration of the hypothetical antagonist that results in loss of 50% of the maximal effect due to tolerance
K_{ant_0}	=	first order rate of appearance or disappearance of tolerance

* C.V.% = coefficient of variation

Of considerable mechanistic interest is that the free fatty acid response to nicotine did not demonstrate tolerance. Nicotine releases free fatty acids from triglycerides and adipose tissue, presumably via an adrenergic mechanism. Free fatty acids are rapidly cleared from the plasma, so in general free fatty acid levels reflect the release rate, and therefore would be a marker of nicotine-mediated lipolysis. The discordance between the pharmacodynamics of nicotine

action on adipose tissue, that is, lipolysis, and that on epinephrine concentration suggests that epinephrine is not responsible for lipolysis. The discordance between nicotine effect on lipolysis and energy expenditure (metabolic rate) suggests that lipolysis with futile cycling of free fatty acids (proposed as a mechanism for adrenergically-mediated increases in energy expenditure) is not the mechanism for the nicotine action to increase metabolic rate.

The difference in rate and extent of development of tolerance to various nicotine responses may reflect nicotine acting on different nicotinic receptor subtypes, which have been reported to exhibit different rates of desensitization *in vitro*, and/or to different homeostatic responses [24].

IMPLICATIONS OF TOLERANCE

For drugs in general, findings of the development of tolerance have implications for the level or frequency of drug dosing. For example, narcotic analgesics need to be dosed at higher levels and either at greater frequency or using sustained release preparations in patients with chronic pain. For cardiac nitrates, continuous dosing with transdermal nitroglycerin is generally avoided [25]. Rather, intermittent doses of oral isosorbide dinitrate or isosorbide mononitrate, or the use of transdermal nicotine for only part of the day, leaving time to regain sensitivity, have become common practices. As mentioned previously, homeostatic tolerance to hypotensive effects of direct vasodilator drugs can be avoided by concomitantly administering diuretics and adrenergic blocking drugs.

Implications for the development of tolerance to nicotine provides other insights into the biological importance of tolerance. The development of tolerance to the noxious effects of nicotine exposure from smoking the first few cigarettes is essential for the continuation of smoking behavior. Without the development of tolerance to noxious effects, no one would smoke and there would be no smoking-related disease. As described previously, tolerance is linked to the development of physical dependence, which contributes to addiction. The temporal aspects of tolerance are likely to influence when a smoker smokes his or her next cigarette. Smoking cigarettes too closely together in time makes no sense when there is still a high degree of tolerance to the rewarding effects of the cigarette. Presumably, the smoker learns an optimal time to smoke the next cigarette when he or she can experience rewarding effects without a high level of residual tolerance, but also before he or she becomes uncomfortable due to withdrawal symptoms that occur when the intercigarette interval is too long. The use of the cigarette as a drug delivery system makes sense because rapid delivery of nicotine to the brain allows the effect to occur before there is time for the development of tolerance. In addition, smoking delivers transient high levels of nicotine to the brain which can overcome prior levels of central nervous system tolerance. Finally, the development of tolerance to cardiovascular responses to nicotine has implications for nicotine use as a medication. High levels of nicotine, such as those seen when one uses nicotine medication and smokes at the same time, is predicted not to produce greater cardiovascular toxicity [15]. This has been confirmed empirically in studies of cigarette smoking combined with intravenous nicotine or high doses of transdermal nicotine [26,27]. Tolerance to the toxic cardiovascular effects of nicotine makes it feasible to use nicotine as a potential harm reduction strategy, that is, using nicotine to decrease the level of cigarette smoking in people who are unable to quit.

CONCLUSION

Tolerance develops to the effects of many drugs, particularly psychoactive, analgesic, and cardiovascular drugs. The development of tolerance to drug action is an important consideration in optimizing medical therapy, both with respect to drug dosing and to toxicity. The development of tolerance can be quantitatively characterized in humans using pharmacokinetic-pharmacodynamic models, several of which have been discussed. Such quantitative studies may be useful in the design of medication regimens for patients who are likely to develop tolerance. Studies of tolerance may also provide mechanistic information on drug action and may provide clues to modifying the development of tolerance.

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REFERENCES

1. Colpaert FC. Drug discrimination: No evidence for tolerance to opiates. Pharmacol Rev 1995;47:605-629.
2. Holford NHG, Sheiner LB. Understanding the dose-effect relationship: Clinical application of pharmacokinetic-pharmacodynamic models. Clin Pharmacokinetics 1981;6:429-453.
3. Kalant H, LeBlanc AE, Gibbins RJ. Tolerance to, and dependence on, some non-opiate psychotropic drugs. Pharmacol Rev 1971;23:135-191.
4. Insel PA. Adrenergic receptors - Evolving concepts and clinical implications. N Engl J Med 1996;334:580-585.
5. Marks MJ, Burch JB, Collins AC. Effects of chronic nicotine infusion on tolerance development and nicotinic receptors. J Pharmacol Exp Ther 1983;226:817-825.
6. Packer M, Meller J, Medina N, Yushak M, Gorlin R. Determinants of drug response in severe chronic heart failure. 1. Activation of vasoconstrictor forces during vasodilator therapy. Circulation 1981;64:506-514.
7. Benowitz NL. Pharmacology of nicotine: Addiction and therapeutics. Annu Rev Pharmacol Toxicol 1996;36:597-613.
8. Benowitz NL, Porchet H, Jacob P, III. Nicotine dependence and tolerance in man: pharmacokinetic and pharmacodynamic investigations. In: Nordberg A, Fuxe K, Holmstedt B, Sundwell A, (eds.) Progress in Brain Research, Vol. 79. Amsterdam: Elsevier Science Publishers, 1989;279-287.
9. Lena C, Changeux J-P. Allosteric modulations of the nicotinic acetylcholine receptor. Trends Neurosci 1993;16:181-186.
10. Madhok TC, Beyer HS, Sharp BM. Protein kinase A regulates nicotinic cholinergic receptors and subunit messenger ribonucleic acids in PC 12 cells. Endocrinology 1994;134:91-96.
11. Benowitz NL, Jacob P, III, Jones RT, Rosenberg J. Interindividual variability in the metabolism and cardiovascular effects of nicotine in man. J Pharmacol Exp Ther 1982;221:368-372.

12. Galeazzi RL, Benet LZ, Sheiner LB. Relationship between the pharmacokinetics and pharmacodynamics of procainamide. Clin Pharmacol Ther 1976;20:278-289.
13. Gourlay SG, Benowitz NL. Arteriovenous differences in plasma concentration of nicotine and catecholamines and related cardiovascular effects after smoking, nicotine nasal spray, and intravenous nicotine. Clin Pharmacol Ther 1997;62:453-463.
14. Porchet HC, Benowitz NL, Sheiner LB, Copeland JR. Apparent tolerance to the acute effect of nicotine results in part from distribution kinetics. J Clin Invest 1987;80:1466-1471.
15. Porchet HC, Benowitz NL, Sheiner LB. Pharmacodynamic model of tolerance: Application to nicotine. J Pharmacol Exp Ther 1988;244:231-236.
16. Shi J, Benowitz NL, Denaro CP, Sheiner LB. Pharmacokinetic-pharmacodynamic modeling of caffeine: Tolerance to pressor effects. Clin Pharmacol Ther 1993;53:6-14.
17. Fattinger K, Verotta D, Benowitz NL. Pharmacodynamics of acute tolerance to multiple nicotinic effects in humans. J Pharmacol Exp Ther 1997;281:1238-1246.
18. Chow MJ, Ambre JJ, Ruo TI, Atkinson AJ, Bowsher DJ, Fischman MW. Kinetics of cocaine distribution, elimination, and chronotropic effects. Clin Pharmacol Ther 1985;38:318-324.
19. Gardmark M, Ekblom M, Bouw R, Hammarlund-Udenaes M. Quantification of effect delay and acute tolerance development to morphine in the rat. J Pharmacol Exp Ther 1993;267:1061-1067.
20. Wakelkamp M, Alvan G, Gabrielsson J, Paintaud G. Pharmacodynamic modeling of furosemide tolerance after multiple intravenous administration. Clin Pharmacol Ther 1996;60:75-88.
21. Mandema JW, Wada RD. Pharmacodynamic model for acute tolerance development to the electroencephalographic effects of alfentanil in the rat. J Pharmacol Exp Ther 1995;275:1185-1194.
22. Bauer JA, Fung H-L. Pharmacodynamic models of nitroglycerin-induced hemodynamic tolerance in experimental heart failure. Pharmaceut Res 1994;11:816-823.
23. Benowitz NL, Kuyt F, Jacob P, III. Influence of nicotine on cardiovascular and hormonal effects of cigarette smoking. Clin Pharmacol Ther 1984;36:74-81.
24. Olale F, Gerzanich V, Kuryatov A, Wang F, Lindstrom J. Chronic nicotine exposure differentially affects the function of human $\alpha 3$, $\alpha 4$, and $\alpha 7$ neuronal nicotinic receptor subtypes. J Pharmacol Exp Ther 1997;283:675-683.
25. Parker JO, Amies MH, Hawkinson RW, Heilman JM, Hougham AJ, Vollmer MC, Wilson RR. Intermittent transdermal nitroglycerin therapy in angina pectoris. Circulation 1995;91:1368-1374.
26. Benowitz NL, Jacob P, III. Intravenous nicotine replacement suppresses nicotine intake from cigarette smoking. J Pharmacol Exp Ther 1990;254:1000-1005.
27. Zevin S, Jacob P, III, Benowitz NL. Dose-related cardiovascular and endocrine effects of transdermal nicotine. Clin Pharmacol Ther 1998;64:87-95.

Discussion: Tolerance as a modulator of drug response

M. Lader:
Some of the phenomena you have presented on nicotine studies could be very similar for benzodiazepines. For example, tolerance phenomena are observed quite quickly after an overdose of benzodiazepines. There is also evidence for the benzodiazepine receptors, that with continual use, different subunits are synthesised, and the sensitivity of the receptor changes. Do you think this has something to do with the type of the receptor, as a generic property of these trans-membranal receptors, or do you think it is specific for individual drugs?

N.L. Benowitz:
I do not know enough about the benzodiazepine receptor to answer that question.

U. Klotz:
Concerning the benzodiazepine receptors, many years ago there were several animal experiments, some of them in monkeys, where they could reset the receptors with the antagonist flumazenil. It was thought that the receptors could be reset to their original naive state by giving every second day an antagonist. Do you know if something similar has been tried later on with other drugs or receptors?

N.L. Benowitz:
It certainly has been done with opiates. There are people who have either been opiate addicts or have been chronically taking opiates in large amounts who have been brought into hospital, put under anaesthesia and given naloxone in high concentrations to resensitise them or to allow them to start on long-term opiate antagonists for therapy for opiate addiction. I do not know if flumazenil has been used in a similar manner for benzodiazepine dependence problems.

M. Lader:
There have been two studies. I did a pilot study which was successful in about 50% of cases. It was followed up in Sweden with a properly controlled study, which suggested that there was some benefit. Those patients who had persistent benzodiazepine withdrawal syndrome apparently continued after the acute withdrawal, and they seemed to benefit from this resetting. But the data are fragmentary and further studies are needed on this issue. The other thing you mentioned was rapid detoxification. This involves all sorts of commercial issues because people tried to patent it. There are also attempts now to do the same paradigm with the benzodiazepines as well, and I think that is much more dangerous. If you give an antagonist to an opioid user, you will get a reaction, but you will not get a potentially fatal one as could happen if flumazenil is given to someone who has been on high doses of benzodiazepines.

L. Aarons:
Although you describe them as mechanistic models, the antimetabolite model is essentially an empirical model. Could you comment on the use of empirical models for the management

or the interpretation of tolerance data, particularly if you move out of nicotine into some therapeutic area? Is it possible that you will take an incorrect decision if you do not know the full mechanistic basis of tolerance?

N.L. Benowitz:

Ours was equivalent to a receptor model. We were interested in using this model to study tolerance in individual subjects but this was not done because of the wide within subject variability in the response. One can model tolerance in an individual and can examine if the model can predict a perturbation in the system. A physiological model cannot be used for some of these responses. If you know there is a homeostatic response, for example, a compensatory vasoconstriction response to a vasodilator, one can develop a physiological (homeostatic) model. It is harder to test for some of the receptor models, because you do not know enough about the kinetics of drug-receptor interactions or the mechanism by which tolerance develops.

P. du Souich:

It should be taken into account that tolerance is not always bad, because sometimes we can induce tolerance to avoid an adverse effect. In the case of benzodiazepines, alprazolam for example, a slow release formulation can be used to decrease the sedative effect. On the other hand, we are all aware of the huge doses of morphine we need to administer to people with burns or in other painful situations. It was proposed that the presence of the 3-glucuronide metabolite could play a role in this tolerance. Do you know anything else about this morphine problem?

N.L. Benowitz:

I do not know about morphine with respect to tolerance. Certainly morphine-6-glucuronide has been thought to play a role in terms of persistence of opiate effects over time, effects such as unexpected respiratory depression occurring during long-term morphine exposure, even when morphine levels are constant. It has been suggested that morphine-glucuronide has a pharmacological role, but I am not aware of its contribution to tolerance.

P. du Souich:

The tolerance I mentioned must be a pharmacokinetic tolerance, because the 3-glucuronide metabolite of morphine is a much weaker agonist or even an antagonist.