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Interchangeability and Predictive Performance of Empirical Tolerance Models

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Contents

Abstract

Models of tolerance are commonly derived on empirical grounds, because of lack of knowledge about the mechanism of tolerance or because of the difficulty of appropriately simplifying complex physiological processes. The present study was performed to evaluate the interchangeability of tolerance models used in the literature and to address some determinants for selection of an appropriate design and data analysis strategy.

Seven models were chosen (noncompetitive antagonist model, partial agonist model, reverse agonist model, direct moderator model, indirect moderator model, pool model and adaptive pool model) along with their corresponding parameter estimates, representing a wide range of empirical models.

The performance of the models on various data sets was evaluated. Data were simulated from each original model and were further analysed by the other models. The effect-time course of each and every data set could be described well by at least 2 different empirical tolerance models, but no model could describe all the data sets adequately. However, all models could adequately describe at least 2 different data sets. This indicates that, without additional knowledge or

assumptions, it is unlikely that reliable mechanistic information can be deduced from the mere fact that 1 (or more) of these models can describe the data. Generally, data expressing only limited tolerance can be described by a wide variety of models, whereas few models will be appropriate for data characterised by extensive tolerance.

The models that gave an adequate description of a data set were selected for further study that investigated their predictive capacity based on the parameters previously determined. Predictions were made for 4 different administration schemes. The selected models gave similar predictions for the extended designs of 3 data sets for which the original study designs characterised tolerance well. For the other 4 data sets, the selected models gave disparate predictions, although the models described the original data set well. Thus, the predictive capability of a model was linked to the original study design, whereas the correlation between predictive performance and the type of model was weak or absent. Based on the results, factors of importance for the design and evaluation of studies of tolerance were identified and discussed.

Tolerance and physical dependence are phenomena that have been described for several drugs. They are manifested as time-variant concentration-effect patterns and originate from different kinds of adaptive processes in the body. Depending on the rate and extent of their development, tolerance and physical dependence may necessitate changes in the dosage regimen of a drug.

Castañeda-Hernández and colleagues divided tolerance into 'true' tolerance, in which the measured effect is subject to tolerance, and 'homeostatic' tolerance, where the measured effect is the outcome of the direct drug effect and homeostatic counter-regulatory processes.[1] Tolerance may be due to 'neuroadaptive' processes, for example uncoupling of the receptor-effector system, reduction of the number of receptors or depletion of second messengers.[2] Homeostatic tolerance could be caused by systemic adaptations of physiological systems, e.g. neurohormonal counter-regulation, as for the vasoconstrictive effect of nitroglycerin[2] or the remoxipride-induced depletion of prolactin.[3]

An often-used definition of neuroadaptive tolerance is that a given dose of a drug produces a decreased effect after repeated administration or, conversely, that increasingly larger doses must be taken to obtain the effects observed with the first dose.[4-7] A rapid, within minutes, diminution of the response has been referred to as desensitisation or tachyphylaxis.[4,8] A general description of tolerance can simply be a decreased effect with prolonged exposure to the drug.[8,9]

Physical dependence is a state in which the presence of a drug is required to maintain the normal physiological system. It is characterised by specific symptoms, withdrawal effects or rebound effects, which arise upon discontinuation of the drug and generally counteract the initial effects of the drug.[5,6,8] Tolerance and physical dependence are commonly, but not necessarily, associated.[4,6]

For simplicity, in this study all adaptive processes influencing the measured effect will be referred to as tolerance, and subsequent discontinuation of the drug as rebound effects. Several publications have characterised and quantified drug tolerance and rebound effects using pharmacokinetic-pharmacodynamic modelling. The division of the models into different types in table I is roughly based on the classification made in the references. The proposed models are more or less empirical with respect to drug mechanisms. Although some models are characterised as physiological when describing certain drug effects, they have all been suggested for more empirical characterisation of other drugs. Often the tolerance mechanism is not fully known or is very complex, which explains

why highly physiological models might be difficult to develop. Few publications have presented comparisons of the performance of different empirical tolerance models.[15,16,28] In addition, there is a lack of information on the applicability of the models to characterise systems and administration regimens other than for the conditions under which they have been developed.

The main objectives of the present study were to:

- evaluate the interchangeability of tolerance models when applied to data sets demonstrating various extents of tolerance
- address the characteristics of the models and their predictive performance when applied to other drug input designs.

Secondary objectives were to:

Table I. Summary of tolerance models in the literature by model type

Tolerance driving force	Predicts rebound?	Designed for tolerance?	Drug	Measured effect	Study time scale	Reference
Tolerance compartment						
Concentration	No	Yes	Furosemide (frusemide)	Cl^- excretion rate; diuresis	< day	10
Concentration	No	Yes	Nicotine	Heart rate	< day	9[a]
Concentration	No	Yes	Nicotine	Heart rate	< day	11
Effect	Yes	Yes	Caffeine	MAP	< day	12
Concentration	Yes	Yes	Morphine	Antinociceptive effect	> day	13
Concentration	Yes	Yes	Morphine	Antinociceptive effect	< day	14[a]
Concentration	No	Yes	Morphine	Antinociceptive effect	> day	15[a]
Concentration	No	Yes	Nicotine	MAP; epinephrine (adrenaline); heart rate	< day	16
Concentration	Yes	Yes	Alprazolam	Timing performance	< day	17
Concentration	Yes	Yes	Cocaine	Timing performance	< day	18
Indirect models						
Concentration	Yes	Yes		Histamine; cAMP	< day	19
Effect	Yes	Yes	Cocaine	Euphoria; heart rate; blood pressure	< day	20
Effect	Yes	Yes	Glyceryl trinitrate	Diastolic pressure	< day	2
Effect	Yes	Yes	Glucocorticoid	mRNA; TAT enzyme	< day	21
Concentration	Yes	Yes	Remoxipride	Prolactin concentration	> day	3[a]
Effect	Yes	Yes	Furosemide	Diuresis; natriuresis	< day	22[a]
Concentration	Yes	No	Morphine	Antinociceptive effect	< day	23[a]
Effect	Yes	Yes	(Simulation)			24
Effect	Yes	Yes	Glucocorticoids	mRNA; TAT enzyme	> day	25
Endogenous control systems						
Concentration	Yes	Yes	Nifedipine	Heart rate; MAP	< day	26
Effect	Yes	Yes	Alfentanil	EEG; ECG; CO_2; respiration	< day	27
Effect	Yes	Yes	Alfentanil	EEG	< day	28[a]
Effect	Yes	Yes	Antide	Testosterone; LH	> day	29
Other models						
Time	No	Yes	Cocaine	Heart rate	< day	30
ND	No	Yes	Alprazolam	Psychomotor performance	< day	31
Time	No	Yes	Cocaine	Heart rate; subjective effect	< day	32
Effect	Yes	Yes	L-Propranolol	Heart rate	< day	33

a Included as part of this article.

cAMP = adenosine 3′,5′-cyclic monophosphate; **Cl^-** = chloride ion; **CO_2** = carbon dioxide; **ECG** = electrocardiogram; **EEG** = electroencephalogram; **LH** = luteinising hormone; **MAP** = mean arterial blood pressure; **mRNA** = messenger RNA; **ND** = not detected; **TAT** = tyrosine aminotransferase.

- provide a comprehensive summary of empirical tolerance models
- distinguish some design characteristics of importance to tolerance studies
- if possible, make suggestions for the model selection process in drug tolerance studies.

1. Theory

Seven tolerance models were selected, and are shown in table II. They were all considered to be general and not restricted to a particular drug action. It should be noted that the nomenclature in several models has been changed from that in the original references in order to standardise the presentation.

In 3 of the models (noncompetitive antagonist model, partial agonist model and reverse agonist model), tolerance was described by a tolerance compartment linked to the plasma compartment, and the time course of tolerance was estimated by the equilibration rate constant (k_{t0}). In the *noncompetitive antagonist* model presented by Porchet et al.,[9] the extent of tolerance to the effect of nicotine on heart rate was described assuming the development of a noncompetitive antagonist. Ouellet and Pollack[15] presented a model for morphine effects (the *partial agonist* model). Tolerance was included in the pharmacodynamic model as a partial agonist, where maximum effect (E_{max}), steady-state concentration of the drug producing 50% of E_{max} (EC_{50}) and γ_E (slope factor of the sigmoid effect curve) denote the parameters that describe the agonist concentration-effect relationship. Maximal tolerance (T_{max}) and steady-state concentration at half the maximal tolerance (TC_{50}) are the parameters characterising the concentration-effect relationship of the partial agonist, i.e. the degree of tolerance. In a somewhat different model for the antinociceptive effects of morphine, called the *reverse agonist* model by Gårdmark and associates,[14] tolerance was defined using an agonist/reverse agonist relationship.

A physiology-mimicking pharmacodynamic model was developed to characterise the development of tolerance to the electroencephalographic effects of alfentanil (the *direct moderator* model).[28] Tolerance was described as a negative feedback (E_f) produced by the drug-induced effect using a first order transfer function. The net effect (E) is the sum of the primary drug effect, described by a sigmoid E_{max} model, and the opposite feedback effect, in which the extent of tolerance is quantified by the parameter G.

An alternative model based on the indirect-response model, the *indirect moderator* model, was presented by Holford and colleagues for the modelling of cocaine data.[20,34] The model originates from the field of hormone regulation,[35,36] and was further evaluated by Gabrielsson and Weiner[37] and applied to the diuretic and natriuretic effects of furosemide (frusemide).[22] The drug was postulated to reduce the loss of response, manifested as an increase in effect. This was counteracted by an integrated stimulating function of a moderator (T), which thereby accounted for the development of tolerance.

Tolerance to drug effects has also been characterised by a physiological model developed by Ekblad and Licko.[19] Movin-Osswald and Hammarlund-Udenaes[3] used the model to describe the time-dependent effect of remoxipride on prolactin concentrations (the *pool* model). In this model, unlike the tolerance compartment models, mass is transferred from the pool to account for the response following drug administration. The rate and extent of pool depletion can characterise a tolerance development process. The drug stimulates the emptying of the pool by the function $S(C_p)$, where C_p is plasma concentration. To account for any differences in the extent of tolerance and rebound development, a feedback loop was added to the previous model, resulting in the model here called the *adaptive pool* model and used to characterise morphine tolerance.[23] In this model, the feedback acts to modify the input rate into the pool as a function of the pool content, with ϕ being the parameter by which an estimation of the degree of feedback is made.

Table II. Selected applications of different tolerance models

Model	Functions[a]	Data	Reference for data
Noncompetitive antagonist[b]	$E = E_0 + \frac{SL_E \cdot C_p}{1 + \frac{C_t}{TC_{50}}}$	Nicotine	9
Partial agonist[b,c]	$E = \frac{E_{max} \cdot C_e^{\gamma E} \cdot TC_{50} + T_{max} \cdot C_t \cdot EC_{50}^{\gamma E}}{EC_{50}^{\gamma E} \cdot TC_{50} + EC_{50}^{\gamma E} \cdot C_t + TC_{50} \cdot C_e^{\gamma E}}$	Morphine (long infusion)	15
Reverse agonist[b,c]	$E = SL_E \cdot C_e - \frac{T_{max} \cdot C_t^{\gamma T}}{TC_{50}^{\gamma T} + C_t^{\gamma T}}$	Morphine (short infusion)	14
Direct moderator[c]	$\frac{dE_f}{dt} = G \cdot k_{t0} \cdot (E - E_f)$ $dE = \frac{E_{max} \cdot C_e^{\gamma E}}{EC_{50}^{\gamma E} + C_e^{\gamma E}} + E_0 - E_f$	Alfentanil	28
Indirect moderator	$\frac{dE}{dt} = k_{in} - k_{out} \cdot E \cdot I(C_p) \cdot S(T)$ $\frac{dT}{dt} = k_{tol} \cdot (E - T)$ $I(C_p) = 1 - \frac{I_{max} \cdot ER}{IC_{50} + ER}$ $S(T) = 1 + \frac{T}{TC_{50}}$	Furosemide (frusemide)	22
Pool	$\frac{dPool}{dt} = k_0 - k_{in} \cdot Pool \cdot S(C_p)$ $\frac{dE}{dt} = k_{in} \cdot Pool \cdot S(C_p) - k_{out} \cdot E$ $S(C_p) = 1 + SL_E \cdot C_p$	Remoxipride	3
Adaptive pool	$\frac{dPool}{dt} = k_0 \cdot \left(\frac{Pool_0}{Pool}\right)^{\varphi} - k_{in} \cdot Pool \cdot S(C_p)$ $\frac{dE}{dt} = k_{in} \cdot Pool \cdot S(C_p) - k_{out} \cdot E$ $S(C_p) = 1 + SL_E \cdot C_p$	Morphine/morphine-3-glucuronide	23

a Some parameters are renamed compared with the original reference.

b Equilibration between plasma and tolerance site, described by $\frac{dC_t}{dt} = k_{t0} \cdot (C_p - C_t)$.

c Equilibration between plasma and effect site, described by $\frac{dC_e}{dt} = k_{e0} \cdot (C_p - C_e)$.

C_e = concentration in the effect compartment; **C_p** = concentration in plasma; **C_t** = concentration in the tolerance compartment; **E** = effect; **E_0** = baseline effect; **EC_{50}** = concentration at half the maximal stimulating effect; **E_f** = tolerance development; **E_{max}** = maximal stimulating effect of the drug; **ER** = excretion rate of the drug in urine; ϕ = exponent of the feedback relationship; **G** = extent of tolerance development; **g** = slope factor of the sigmoid effect curve; **I()** = inhibition function; **IC_{50}** = concentration at half the maximal inhibiting effect; **I_{max}** = maximal inhibiting effect of the drug; **k_0** = rate constant for production of the pool; **k_{e0}** = rate constant out of the effect compartment which determines the rate of the effect delay; **k_g** = rate of tolerance development; **k_{in}** = rate constant for production of effect; **k_{out}** = rate constant for loss of effect; **k_{t0}** = rate constant out of the tolerance compartment which determines the rate of the tolerance delay; **$Pool_0$** = baseline amount in the pool; **S()** = stimulation function; **SL_E** = slope of the linear effect; **SL_T** = slope of the tolerance relationship; **T** = tolerance moderator; **TC_{50}** = steady-state concentration at half the maximal tolerance; **T_{max}** = maximal tolerance.

2. Methods

The study was divided into 2 parts. Part I was conducted to evaluate the performance of the 7 empirical tolerance models on various data sets. Data were simulated from each original model and were further analysed by the other 6 models. The models

that gave an adequate description of a data set were selected for part II. The objective of Part II was to demonstrate the predictive capacity of the selected models based on the parameters obtained from part I, with different study designs.

2.1 Part I

2.1.1 Simulations

For each selected model, error-free concentration and effect data were simulated for a typical patient according to the study design of the original reference. The simulations were based on the model parameters displayed in table III, which generally were the estimates presented in the original reference. Concentration and effect data were simulated without error at the same time-points as in the original reference. However, as indicated in table III, modifications to the original work had to be made in some instances because the kinetics and dynamics could not be fully recapitulated from the parameters given in the reference.

The plasma concentrations in the morphine long infusion study (partial agonist model) were simulated using a 1-compartment model to attain the midpoints of the concentration intervals presented in the reference.[15] To simulate the pharmacodynamics of alfentanil (direct moderator model), the baseline effect (7Hz) was taken from the effect-time diagrams and the corresponding baseline effect (E_0) was calculated to 15Hz according to the reference.[28] The furosemide excretion rate profile was assessed following linear interpolation of the raw data from 1 individual (subject 1), kindly supplied by the authors, and served as the input to the indirect moderator model simulations.[22] The kinetics of remoxipride in the pool model were described in the original reference by a 2-compartment model.[3] However, there was no information regarding the parameters for the biexponential equation in the reference and, as the distribution phase was small, 1-compartment kinetics were selected, as shown to be appropriate in other studies of remoxipride.[38] When the morphine short infusion data were simulated (the adaptive pool model), modifications were made with respect to the pharmacodynamics.[23] The parameters used in this study correspond to the morphine infusion only and differ, therefore, somewhat from the parameters in the original reference.

2.1.2 Analysis of the Simulated Data

In a second step, each of the simulated effect-time profiles was analysed by all 7 models. Generally, in order to obtain the best fit to the data by each model, all models were allowed to change in terms of different pharmacodynamic relationships, such as the E_{max} model or a linear relationship.

In the tolerance compartment models, the equilibration delay (k_{e0}) was included or removed depending on the nature of the data. When the indirect moderator model was applied to the various data sets, the drug-induced stimulation or inhibition was tested on both the production and the loss of response to obtain the best fit. In addition, flexibility was further increased by modelling tolerance as either inhibition of production of response or stimulation of loss of response, respectively.

Two modifications were made to the indirect moderator model presented for furosemide.[22] The indirect moderator model in the original reference estimates 2 parameters that both describe the rate of tolerance, k_{tol} and tolerance lag-time (T_{tol}), while fixing the parameter relating to the extent of tolerance (TC_{50}) at a value of 1.[22] Rather than fixing the extent of tolerance to a predetermined value, which limited the generality of the model, the parameter TC_{50} and thereby the extent of tolerance at steady state was estimated. The T_{tol} used in the original reference was removed from the model used in the analysis of the other data sets, as estimating 2 parameters was judged to be unrealistic and k_{tol} was the more physiological parameter. Thus, in the present work, when using the indirect moderator model, the rate of tolerance development was characterised by k_{tol} and the extent of tolerance by TC_{50}.

In 2 data sets, the effect was reported as a fraction of the baseline (morphine short infusion)[14] and of baseline and cut-off latency (10 sec) [morphine long infusion)],[15] omitting baseline as a parameter in the models. However, to fit the indirect

Table III. Parameter estimates used in the simulations in Part I

Parameter	Nicotine	Morphine (long infusion)[a]	Morphine (short infusion)	Alfentanil[a,c]	Furosemide (frusemide)[a]	Remoxipride	Morphine/morphine -3-glucuronide[a]
k_{10}	0.0112 min^{-1}		0.08 min^{-1}		2.5 h^{-1}	0.18 h^{-1}	
k_{12}	0.03 min^{-1}		0.13 min^{-1}		1.0 h^{-1}		
k_{21}	0.033 min^{-1}		0.06 min^{-1}		1.33 h^{-1}		
V_c	114 ml		0.229L	174 ml/kg	34.7 ml		
k_{t0}	0.02 min^{-1}	0.005 min^{-1}	0.014 min^{-1}				
SL_E	1.31 beats•min^{-1}•ml^{-1}•ng^{-1}		31.7 %•L•μmol^{-1}			2.3 μg/L/h	1.5 V/μmol/L
TC_{50}	7.72 μg/L	14 μg/L	17 μmol/L		1 ml/min		
E_0	61.2 beats•min^{-1}	2.8%[b]	3[a] min^{-1}	15 μV/sec	8.5 ml/min	13.1 μg/L	4 V
CL		5.4-3.3 L/min					
Vd		0.8 min^{-1}				40L	
k_{e0}		4.33 min^{-1}	0.02 min^{-1}	4 min^{-1}			
E_{max}		100%		72 μV/sec			
EC_{50}		389 μg/L		845 μg/L			
γ_E		2.64		1.85			
T_{max}		7%	713%				
γ_T			3.6				
CL_{max}				49.7 ml/min/kg			
CL_{min}				29.3 ml/min/kg			
K_m				101 μg/L			
CL_2				101 ml/min/kg			
V_2				349 ml/kg			
CL_3				3.26 ml/min/kg			
V_3				149 ml/kg			
k_g				0.1 min^{-1}			
G				1.16			
k_{out}					9 h^{-1}	1.87 h^{-1}	0.35 h^{-1}
k_{tol}					0.1 h^{-1}		
I_{max}					0.81		
IC_{50}					38 μg/min		
T_{tot}					1.2h		
$Pool_0$						245 μg/L	5.77 V
ϕ							0.07

a Modifications of pharmacokinetic/dynamic parameters with respect to the original reference.

b Baseline value taken from Gårdmark et al.[23]

c Pharmacokinetic parameters described in the original article.

CL = clearance; **CL_2** = intercompartmental clearance between compartment 1 and 2; **CL_3** = intercompartmental clearance between compartment 2 and 3; **CL_{max}** = maximum clearance value at low drug concentrations; **CL_{min}** = minimum clearance value at high drug concentrations; **E_0** = baseline effect; **EC_{50}** = concentration at half the maximal stimulating effect; **E_{max}** = maximal stimulating effect of the drug; ϕ = exponent of the feedback relationship; **G** = extent of tolerance development; **γ_E** = slope factor of the sigmoid effect curve; **γ_T** = slope factor of the sigmoid tolerance curve; **IC_{50}** = concentration at half the maximal inhibiting effect; **I_{max}** = maximal inhibiting effect of the drug; **k_{10}** = rate constant out of compartment 1; **k_{12}** = rate constant from compartment 1 to 2; **k_{21}** = rate constant from compartment 2 to 1; **k_{e0}** = rate constant out of the effect compartment which determines the rate of the effect delay; **k_g** = rate of tolerance development; **k_{in}**= rate constant for production of effect; **Km** = Michaelis-Menten constant; **k_{out}** = rate constant for loss of effect; **k_{t0}** = rate constant out of the tolerance compartment which determines the rate of the tolerance delay; **k_{tol}** = rate constant for the moderator; **$Pool_0$** = baseline amount in the pool; **SL_E** = slope of the linear effect; **SL_T** = slope of the tolerance relationship; **TC_{50}** = steady-state concentration at half the maximal tolerance; **T_{max}** = maximal tolerance; **T_{tol}** = time delay of onset of tolerance; **V_2** = volume of distribution for compartment 2; **V_3** = volume of distribution for compartment 3; **V_c** = initial volume of distribution; **Vd** = volume of distribution.

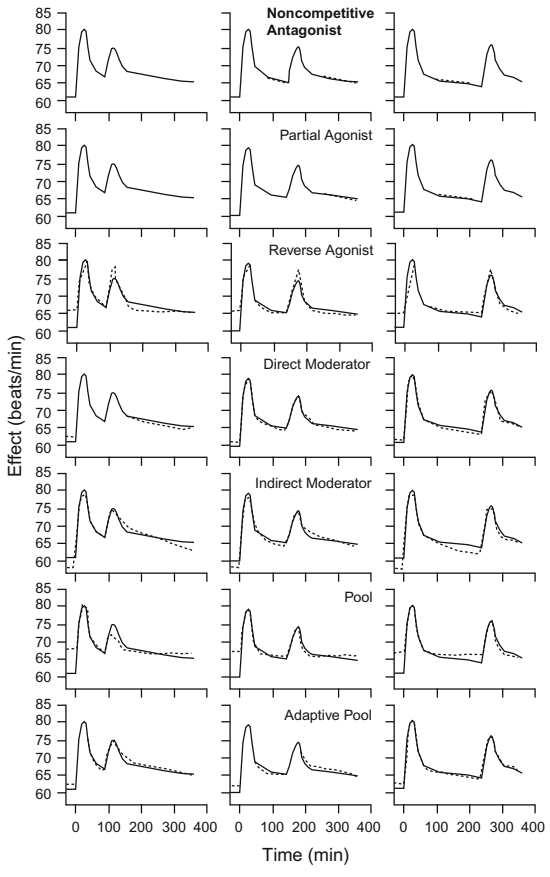

Fig. 1. The effect-time profiles of different empirical tolerance models (broken lines) applied to the nicotine data set[9] originally described by the noncompetitive antagonist model (solid lines). This is from part I of the study.

models, a baseline value is necessary. The baseline value was set at 3V, which was the mean of the baseline observations in the morphine short infusion study.[23] The baseline latency within the morphine long infusion data was assumed to be 2.8 sec, which was the baseline observation obtained for the tail-flick method in our laboratory.[48]

In total, 49 effect-time profiles and parameter sets were obtained, i.e. 7 from each simulated model. In the analysis of all the data sets, a homoscedastic error was assumed.

To obtain an approximate estimate of the extent of tolerance present in the data, the tolerance component in each original model was removed and predictions were made by the reduced models. The original effect-time profile was compared to the profile obtained from the reduced model. The maximal tolerance was taken as the largest absolute difference between the curves divided by the peak effect from the reduced model, corrected for baseline. This estimate is entirely model-dependent and only one of many possible ways of defining the extent of tolerance. Moreover, being a model-dependent estimate, the extent of tolerance is no more reliable than the model itself.

2.1.3 Model Selection

The criterion for evaluating the performance of the different models on each data set was visual inspection of the predicted and simulated observations versus time (figs 1 to 7). The models were judged as overparameterised, and not selected, if the parameter confidence intervals were large (>60% relative standard error) or not obtainable. The models that for each simulated profile fulfilled these 2 criteria were selected for further evaluation in part II.

2.2 Part II

The predictive performance of the models selected in part I was tested by simulating the expected effect-time profiles for 4 different administration regimens, using the pharmacodynamic parameters obtained in part I. Predictions were made for the following administration regimens: (i) 3 consecutive infusions of the same dose; (ii) a stepwise infusion of 4 dose levels; (iii) 3 escalated short infusions; and (iv) a single continuous infusion. The lengths of the input profiles were correlated to the time of tolerance development estimated in part I. In (i) and (iii), the infusion lengths were set to $1 \times t_{½,kt0}$ (i.e. the half-time determined by the tolerance rate constant). The duration of each step in (ii) was $3 \times t_{½,kt0}$. The infusion time of the long infusion (iv) was fixed at $4 \times t_{½,kt0}$. The time between the consecutive doses in (i) was 3 x $t_{½,kt0}$. In the pool model and the adaptive pool model, no tolerance rate constant is estimated. Instead, the input length was based on $t_{½,kin}$ (i.e. the

half-time determined by the rate constant for production of effect). In all designs, the decline was predicted for $10 \times t_{½,kt0}$ (or $10 \times t_{½,kin}$) after discontinuation of the infusions.

The concentration range of the designed profiles was the same as in the original data set. The concentrations were simulated using the pharmacokinetic parameters described in table III, with some modifications. To simulate the input profiles for the 3 models describing morphine effects (the partial agonist model, reverse agonist model and adaptive pool model), the pharmacokinetics of morphine presented by Gårdmark et al.[14] were used. A 2-compartment pharmacokinetic model with first-order input and an absorption lag-time was fitted to raw data (subject 1) for furosemide and the obtained parameters were used to simulate the furosemide concentration profiles.

2.3 Data Analysis

The simulation of data and the subsequent analysis were performed in NONMEM version V.[39] For visual inspection of the results, the Xpose package, version 2,[40] using S-PLUS, version

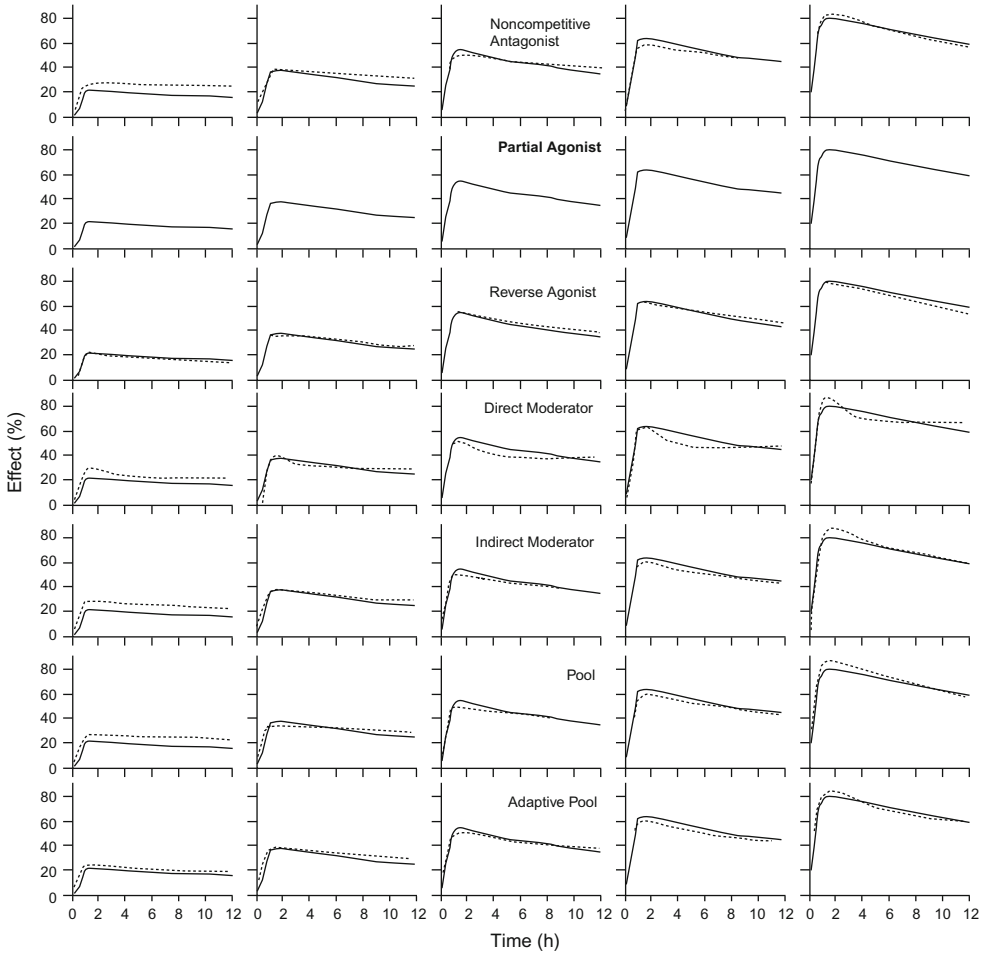

Fig. 2. The effect-time profiles of different empirical tolerance models (broken lines) applied to the morphine long infusion data set[15] originally described by the partial agonist model (solid lines). This is from part I of the study.

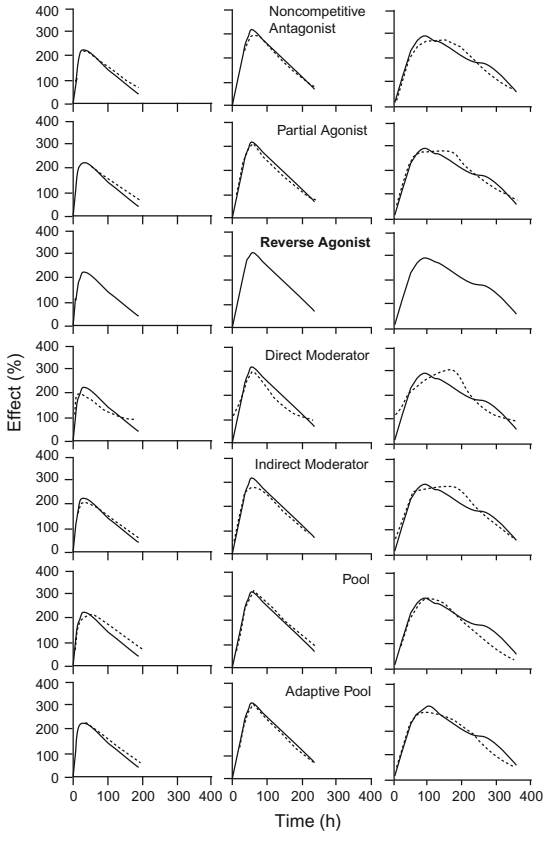

Fig. 3. The effect-time profiles of different empirical tolerance models (broken lines) applied to the morphine short infusion data set[14] originally described by the reverse agonist model (solid lines). This is from part I of the study.

3.4,[41] was applied. The NONMEM subroutines used were ADVAN6, except for the direct moderator model and the indirect moderator model, where ADVAN8 was used.

3. Results

3.1 Part I

The simulated profiles from the original models and the predictions made by the other 6 models for these profiles are presented in figs 1 to 7. The functional forms of the pharmacodynamic relationships that best describe the different data sets are presented in tables IV and V. All models produced a successful termination of the estimation step, although for some runs the standard errors were not obtainable (table VI). The objective function values for each model are presented in table VI, which also highlights the models selected for part II. The results are presented based on the data sets.

3.1.1 Nicotine Data

Three groups received 2 short infusions,[9] (fig. 1) administered with 3 different interdose intervals. Of the 2 resulting peaks, the second peak was reduced because of tolerance. The initial baseline effect (61 beats/min) was not reached at the

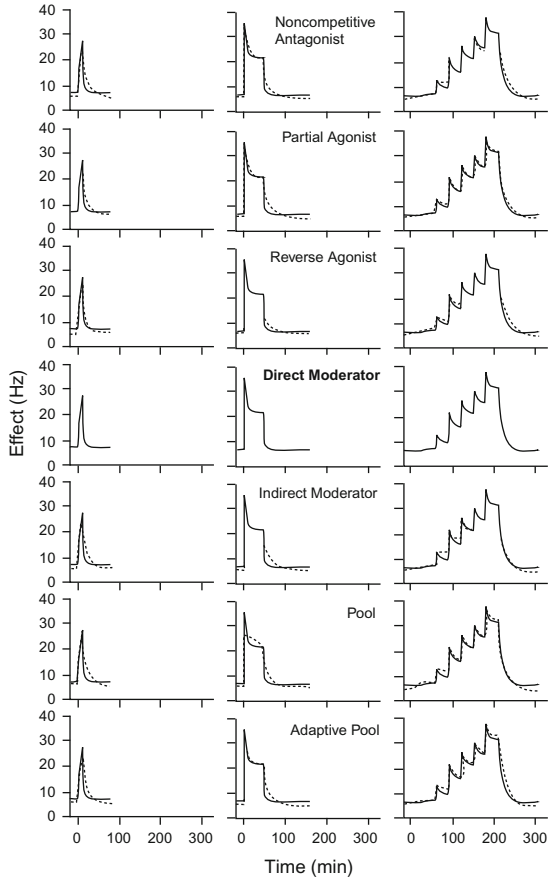

Fig. 4. The effect-time profiles of different empirical tolerance models (broken lines) applied to the alfentanil data set[28] originally described by the direct moderator model (solid lines). This is from part I of the study.

end of the experiment. The partial agonist model was reduced to the original noncompetitive antagonist model. The direct moderator model and adaptive pool model produced good fits, whereas the other models overpredicted the initial baseline, since they could not predict both the initial baseline and the slow terminal decrease in effect. The adaptive pool model produced a significantly better fit compared with the pool model. The extent of tolerance in this data set was estimated to be approximately 74%. Three models (the partial agonist, direct moderator and adaptive pool models) as well as the original model were judged to adequately describe the data (table VI).

3.1.2 Morphine Long Infusion Data

The data set[15] (fig. 2) consisted of 5 continuous infusions of the same duration (over 12 hours). The effect was reduced during all infusions, demonstrating development of tolerance. In the fit of the partial agonist model to its 'own' data, k_{t0} and TC_{50} were poorly estimated with coefficients of variation of 66 and 64%, respectively, which was unique for part I. The tolerance $t_{1/2}$ was very long (5.8 days) as compared with the study time of 12 hours, which contributed to the poor precision of k_{t0}.

The reverse agonist model, using a sigmoid effect relationship, gave the best description of the escalated infusions in this data set, with parameter estimates similar to those in the original model. The other models, apart from the direct moderator model, systematically overpredicted or underpredicted the effect. Inclusion of sigmoidicity in the models did not improve the fits. The direct moderator model predicted the tolerance to develop with a much shorter $t_{1/2}$ than the original model, which resulted in the curvature observed in the predictions.

The adaptive pool model was reduced to the pool model. As in the original reference, E_{max} was fixed at 100% in all models, which for the noncompetitive antagonist model, the pool model and the adaptive pool model resulted in large and unreliable estimates of EC_{50}. The extent of tolerance was estimated as 36%. One model (the reverse agonist

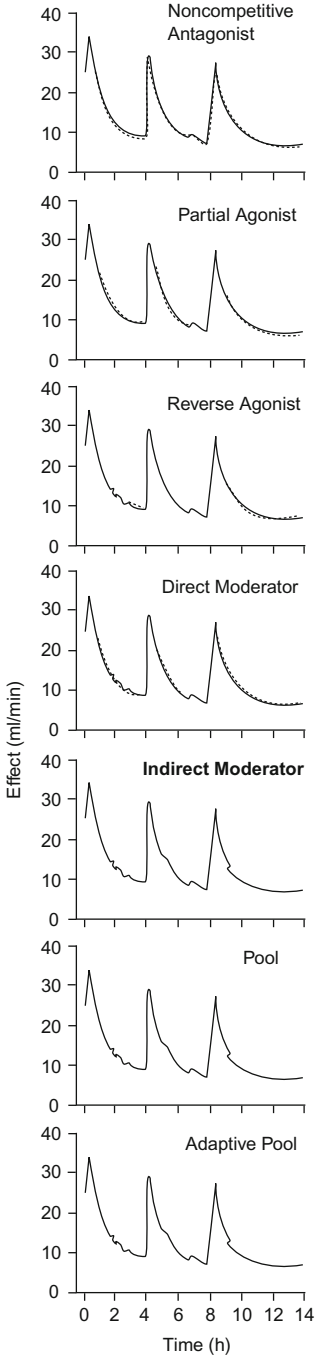

Fig. 5. The effect-time profiles of different empirical tolerance models (broken lines) applied to the furosemide (frusemide) data set[22] originally described by the indirect moderator model (solid lines). This is from part I of the study.

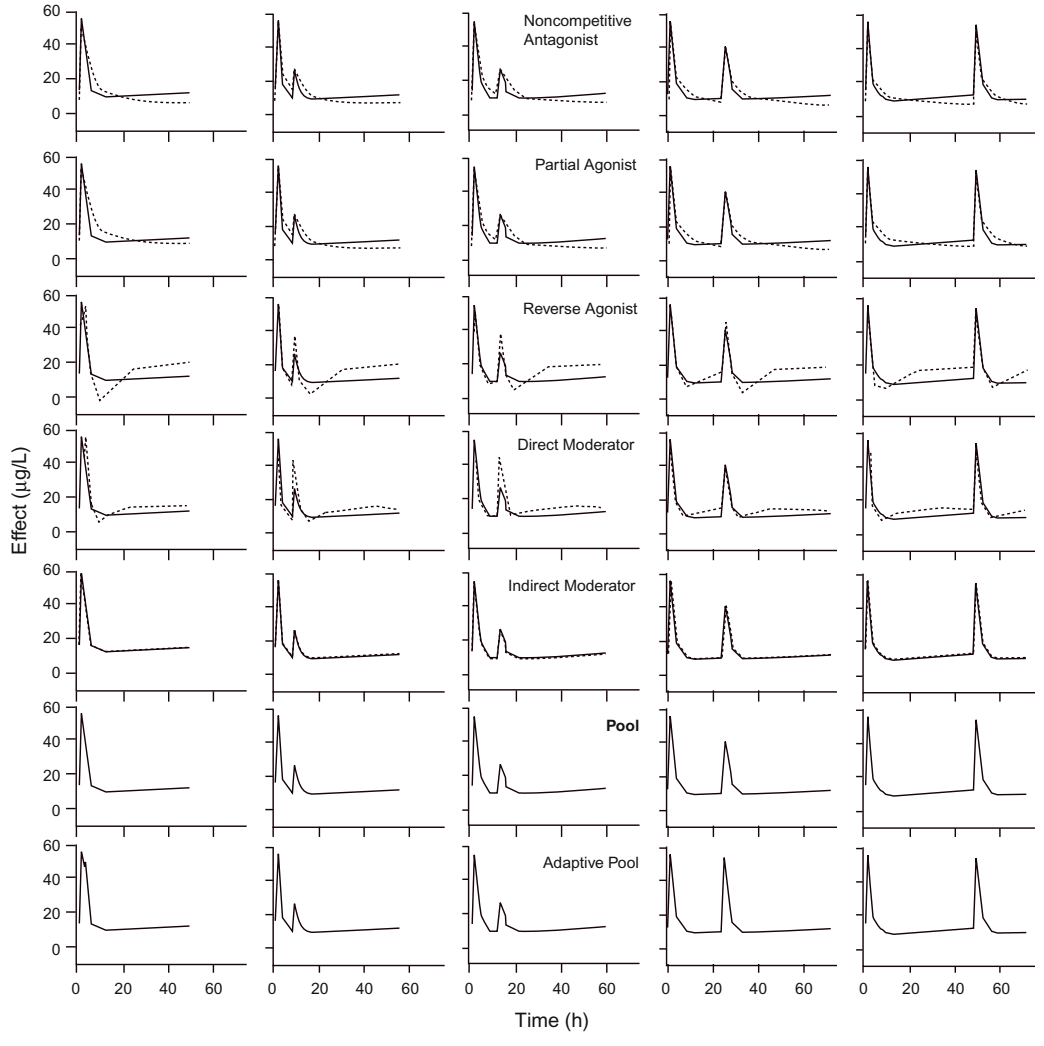

Fig. 6. The effect-time profiles of different empirical tolerance models (broken lines) applied to the remoxipride data set[3] originally described by the pool model (solid lines). This is from part I of the study.

model) was selected for part II as well as the original model (table VI).

3.1.3 Morphine Short Infusion Data

In this data set[14] (fig. 3), 3 separate infusions of different lengths (10 minutes, 1 hour and 3 hours) were combined, with tolerance clearly observed during the longest infusion. The tolerance compartment models together with the adaptive pool model gave the best fit to this data set. The 2 shortest infusions were adequately described with respect to the time and extent of the maximal effect. For the longest infusion, the models generally failed to predict the peak time and the loss of effect. The estimated extent of tolerance in this data set was 63%. Two models (the noncompetitive antagonist model and adaptive pool model), apart from the original model, were selected as acceptably describing the data (table VI).

3.1.4 Alfentanil Data

The regimen consisted of a 10-minute infusion, a computer-controlled 50-minute infusion and a computer-controlled step infusion[28] (fig. 4). The effect data were characterised by a rapid increase to peak effect and a subsequent quick decrease due to development of tolerance. The reverse agonist model and the noncompetitive antagonist model best explained this data set. The partial agonist model was reduced to the noncompetitive antagonist model. The tolerance compartment models were slightly better than the adaptive pool model, which in comparison with the pool model benefited from the feedback function. The extent of tolerance estimated for the data set was 60%. Three models were selected for part II (noncompetitive antagonist model, partial agonist model and reverse agonist model) as well as the original model (table VI).

3.1.5 Furosemide Data

Furosemide[22] (fig. 5) was administered as 3 short infusions of 5 minutes each separated by 4 hours. The data demonstrated only a small reduction in the peak effects, indicating relatively limited development of tolerance. This data set was well described by all models. An effect compartment was added to the plasma compartment to improve the fits of the tolerance compartment models as well as the direct moderator model. The feedback function was not supported by the data and consequently the adaptive pool model was reduced to the pool model. The partial agonist model was also reduced to the noncompetitive antagonist model. The extent of tolerance present in the data was estimated to be 31%. Five models, as well as the original model, adequately described the data and were selected for part II (table VI).

3.1.6 Remoxipride Data

Two 30-minute infusions[3] (fig. 6) were administered separated by different intervals. The shortest interdose interval of 2 hours causes a profound development of tolerance, which decreases as the interdose interval increases up to 48 hours. In addition, the data also demonstrate the development of rebound effects. As expected, the adaptive pool model was overparameterised with respect to the feedback function and was reduced to the pool model used in the original work.

The indirect moderator model resulted in a markedly better fit than the other models. An effect

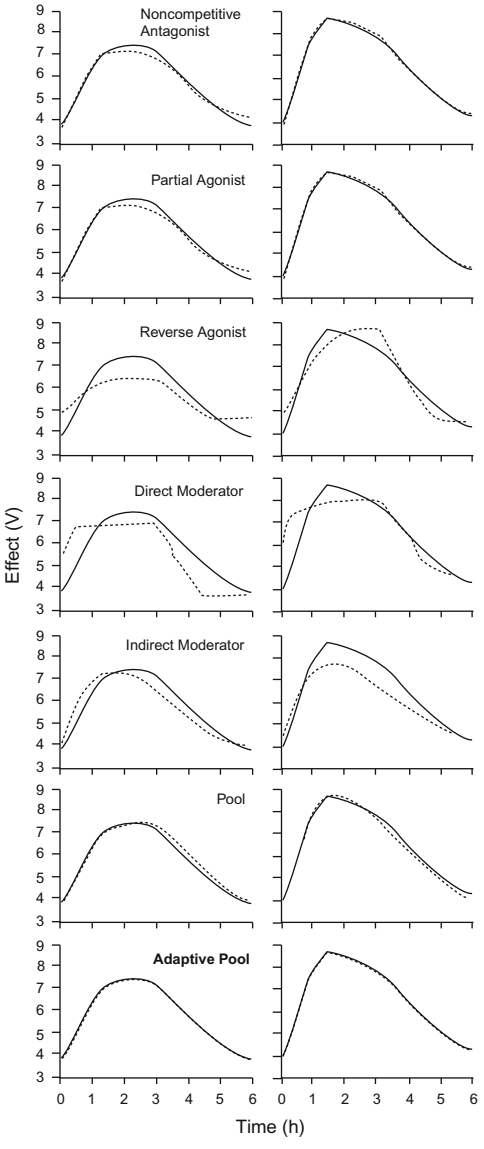

Fig. 7. The effect-time profiles of different empirical tolerance models (broken lines) applied to the morphine/morphine-3-glucuronide data set[23] originally described by the adaptive pool model (solid lines). This is from part I of the study.

Table IV. Functional form of the concentration-effect relationships

Model	Nicotine	Morphine (long infusion)	Morphine (short infusion)	Alfentanil	Furosemide (frusemide)	Remoxipride	Morphine/morphine-3-glucuronide
Noncompetitive antagonist	Linear	Linear	Linear	E_{max}, γ	E_{max}, γ	Linear	Linear
Partial agonist	Linear	E_{max}, γ	Linear	E_{max}, γ	E_{max}	Linear	Linear
Reverse agonist	Linear	E_{max}, γ	Linear	E_{max}	E_{max}, γ	Linear	Linear
Direct moderator	E_{max}	E_{max}	Linear	E_{max}, γ	E_{max}	Linear	Linear
Indirect moderator	E_{max} [a]	I_{max} [b]	I_{max} [b]	Linear	I_{max} [b]	E_{max} [a]	E_{max} [a]
Pool	Linear	E_{max}, γ	Linear	Linear	E_{max}, γ	Linear	Linear
Adaptive pool	Linear	E_{max}	Linear	Linear	E_{max}	Linear	Linear

a Stimulation or inhibition of the production of response (k_{in}).

b Stimulation or inhibition of the loss of response (k_{out}).

E_{max} = maximum effect; **γ** = slope factor of the sigmoid effect curve; **I_{max}** = maximal inhibiting effect of the drug; **k_{in}** = rate constant for production of effect; **k_{out}** = rate constant for loss of effect.

compartment was added to the plasma compartment to improve the fits of the tolerance compartment models as well as the direct moderator model. The rebound effect could not be described by the noncompetitive antagonist model or the partial agonist model, although the noncompetitive antagonist model adequately predicted the peak effects. In contrast, the direct moderator model, and particularly the reverse agonist model, predicted pronounced rebound effects. The data did not support the partial agonist model, which was reduced to the noncompetitive antagonist model. The data set shows a large extent of tolerance, estimated at 91%. Two models (the adaptive pool model and the indirect moderator model), as well as the original model, were selected to be evaluated in part II (table VI).

3.1.7 Morphine/Morphine-3-Glucuronide Data

The data[23] (fig. 7) originate from 2 infusions, of the same duration (3 hours) but with different rates, in which tolerance can be observed. Tolerance was demonstrated by a reduction in the effect already evident during the infusion. The pool model produced a good fit to the data. A similarly good fit was obtained with the noncompetitive antagonist model. The reverse agonist model and direct moderator model both failed to predict the development of tolerance and returned similar objective function values, although the data were mis-specified differently. The partial agonist model was reduced to the noncompetitive antagonist model. The rate constants k_{e0} and k_{t0} were not obtainable for the reverse agonist model and the direct moderator model. Tolerance was estimated to develop

Table V. Functional forms of the concentration-tolerance relationships[a]

Model	Nicotine	Morphine (long infusion)	Morphine (short infusion)	Alfentanil	Furosemide (fursemide)	Remoxipride	Morphine/morphine-3-glucuronide
Noncompetitive antagonist	C_t/TC_{50}	C_t/TC_{50}	C_t/TC_{50}	C_t/TC_{50}	C_t/TC_{50}	C_t/TC_{50}	C_t/TC_{50}
Partial agonist	C_t/TC_{50}	T_{max}	T_{max}	C_t/TC_{50}	T_{max}, γ	C_t/TC_{50}	C_t/TC_{50}
Reverse agonist	Linear	Linear	T_{max}, γ	Linear	Linear	Linear	Linear
Indirect moderator	T_{max} [c]	T_{max} [c]	T_{max} [c]	T_{max} [c]	Linear[c]	Linear[b]	Linear[b]

a The functional forms of the direct moderator model, pool model and adaptive pool model are always as given by the equations in table II.

b Stimulation or inhibition of the production of response (k_{in}).

c Stimulation or inhibition of the loss of response (k_{out}).

C_t = concentration in the tolerance compartment; γ = slope factor of the sigmoid effect curve; **k_{in}** = rate constant for production of effect; **k_{out}** = rate constant for loss of effect.; **TC_{50}** = steady-state concentration at half the maximal tolerance; **T_{max}** = maximal tolerance.

Table VI. Objective function values in the final models from Part I. Values in **bold** indicate that the model was selected for Part II

Model	Nicotine	Morphine (long infusion)	Morphine (short infusion)	Alfentanil	Furosemide (frusemide)	Remoxipride	Morphine/morphine-3-glucuronide
Noncompetitive antagonist	**0**	445[b]	**462**	**1073**	298[b]	968	**170**[b]
Partial agonist	**0**[b,c]	**0**[b]	456[b]	**1073**[c]	**251**	968[c]	**170**[a,c]
Reverse agonist	255	**353**	**0**	**1023**	**267**	1129[b]	323[a]
Direct moderator	**121**	445	533	**0**	**260**	1153	321[a]
Indirect moderator	207	448	504	1144	**0**	**694**	208
Pool	263	426[b]	509	1324	**226**	**0**	**181**
Adaptive pool	**135**	426[b,d]	**447**	1192	**217**	**0**[d]	**0**

a Standard errors not obtainable.
b Large standard error.
c Reduced to the noncompetitive antagonist model.
d Reduced to the pool model.

to the extent of 88%. Three models (the noncompetitive antagonist model, the partial agonist model and the pool model) were selected as adequately describing the data (table VI).

3.2 Part II

This part of the study was performed to evaluate how the models that were judged to give a good description of a data set in Part I predicted the effect of other administration regimens. The predictions were compared with the 'true' profiles, i.e. the predicted effects using the original model. The models that displayed adequate fits to each data set, based on visual inspection and the objective function value, were selected for part II as indicated in table VI. The effect-time profiles following the 4 different inputs are presented in figure 8.

3.2.1 Nicotine Data

The 3 selected models predicted similar profiles as the 'true' noncompetitive antagonist model.[9] For the adaptive pool model, pool depletion increased the influence of the feedback, which is demonstrated in the last step of the stepwise infusion and also in the predictions for the long infusion. Although the declines were followed for 10 $\times t_{½,kt0}$, baseline (61 beats/min) was never attained for any of the models.

3.2.2 Morphine Long Infusion Data

One model was selected, but showed extremely different predictions compared with the 'true' partial agonist model.[15] With both models, the effect site equilibrated much faster with the plasma concentration (approximately 10 minutes) compared with the equilibration half-time between the plasma and tolerance compartments (5.8 days). This, together with a linear model for tolerance, resulted in huge negative predictions from the reverse agonist model. For the partial agonist model, the prediction very slowly approached the baseline following termination of drug administration.

3.2.3 Morphine Short Infusion Data

The adaptive pool model performed similarly to the 'true' reverse agonist model[14] for the different inputs, whereas the noncompetitive antagonist model predicted the effect differently. In the profiles from the noncompetitive antagonist model, tolerance does not seem to develop to the same extent as in the other models, due to a several-fold slower rate of tolerance development. This is particularly obvious during the slow infusion, where the effect increases throughout the infusion.

3.2.4 Alfentanil Data

For alfentanil, the 4 selected models all gave similar predictions to the 'true' direct moderator model,[28] indicating that the data in part I were very informative. There was conformity in the predicted profiles irrespective of input regimen.

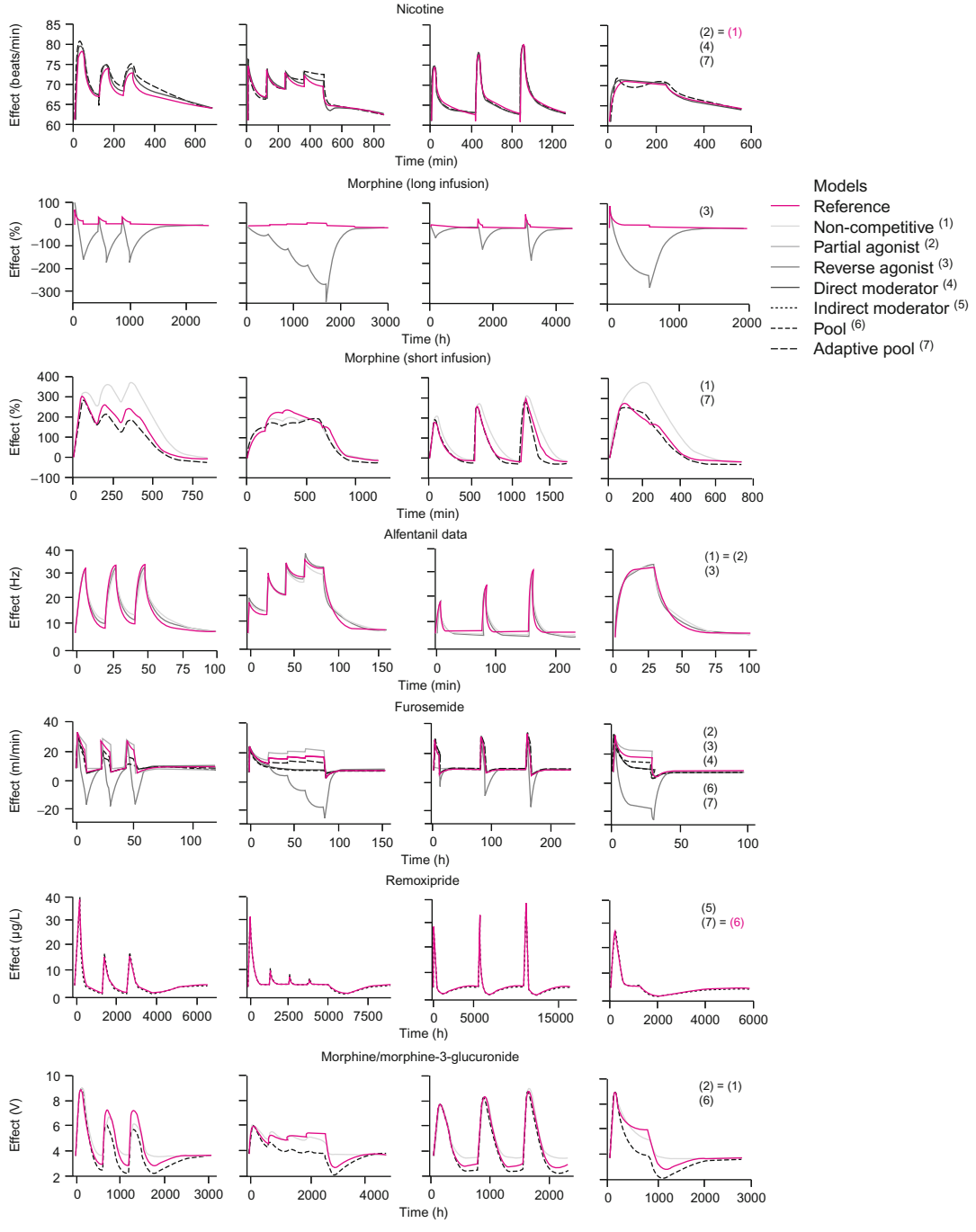

Fig. 8. Predicted effect-time profiles for the models selected in Part I. Each row represents the predictions by the selected models for a particular data set. The columns represent the 4 administration schemes used (from left to right: 3 consecutive infusions of the same dose; stepwise infusion of 4 dose levels; 3 escalated short infusions; single continuous infusion). This is from part II of the study. The selected models are indicated in table VI.

3.2.5 Furosemide Data

For furosemide, the predictions of the 5 selected models show marked differences in comparison with the 'true' indirect moderator model[22] and also between each other. In contrast to what was observed in the original data, the selected models demonstrated a large degree of tolerance development. During the step infusion, the reverse agonist model and the pool model attained baseline values as early as during the first step. All models, except the partial agonist model, demonstrated rebound effects. The predictions of the reverse agonist model resulted in an initial peak effect followed by large negative effects. This peculiar profile is because the positive effect is approaching E_{max} and is counteracted by a large negative tolerance effect. The noncompetitive antagonist model predicted an initial peak effect followed by a decline down to the baseline effect, which is maintained throughout the drug exposure. In this case, the antagonistic influence overrules the agonist effect and subsequently reduces the effect to the baseline effect.

3.2.6 Remoxipride Data

The indirect moderator model behaved similarly to the 'true' pool model[3] during the stepwise, escalated and continuous infusions. At each step of the stepwise infusions, baseline was attained. The last concentration step produced only a slight change in the effect due to the full depletion of the pool (pool model) and a complete inhibition of k_{in} (indirect moderator model). Both models predicted rebound effects when the remoxipride concentration decreased.

3.2.7 Morphine/Morphine-3-Glucuronide Data

The 3 models selected for the morphine/morphine-3-glucuronide data demonstrated different predictions in comparison with the 'true' adaptive pool model.[23] The consecutive infusion regimen allowed the pool in the pool model to be refilled to a certain extent before the next dose, whereas the stepwise and the continuous infusions caused a full depletion of the pool, demonstrated by a pronounced tolerance. The feedback mechanism in the adaptive pool model increased the input rate into the pool, causing less tolerance and rebound. The pool model generally produced larger rebound effects than the adaptive pool model.

4. Discussion

4.1 Models

The present study was performed to evaluate the interchangeability of tolerance models used in the literature and also to address some determinants for selection of an appropriate design and subsequently a suitable model. Models of tolerance are often derived on empirical grounds, because of a lack of knowledge about the mechanism or because the biological system is complex and cannot easily be simplified into a model that can be determined from the available data.

The effect-time course of each data set in part I could be described well by at least 2 different empirical tolerance models. This indicates that without additional knowledge (or assumptions), it is unlikely that reliable mechanistic information can be deduced from the mere fact that one (or more) of these models can describe data. No model could describe all data sets adequately, but all models could describe some data sets well. Moreover, there was no pattern that showed 2 models performing in a consistently similar way in all or most data sets. Nor was there any obvious trend indicating that tolerance compartment models were better than the indirect types of models when applied to data originating from tolerance compartment models, or vice versa. Thus, although different types of tolerance mechanisms were included among the data sets, the models showed little or no correlation with any particular system.

Of the tolerance compartment models, the noncompetitive antagonist model was the most general and was selected for 4 data sets. This model characterises tolerance development based on the formation of an antagonist, but is also representative of other tolerance mechanisms, such as upregulation of receptors.[12] However, the model does not predict rebound effects, which limits its usefulness when such a phenomenon is observed. The partial agonist model could be reduced to the noncompet-

itive antagonist model when fitted to 5 of the data sets, and was only preserved when applied to the furosemide data. In this model, the tolerance effect is quantified by the hypothetical interaction of an agonist and a partial agonist. Thus, if tolerance development is slow in relation to the effect, the contribution of the partial agonist will result in a lingering effect with the duration determined by the tolerance half-life, which can be observed in figure 8 (morphine long infusion data). Hypothetically, in both the noncompetitive antagonist model and the partial agonist model, the equations originate from events occurring at the same receptor.

The third compartment model discussed, the reverse agonist model, consists of 2 'additive' independent effects working in opposite directions, which thus make the prediction of a rebound effect possible. Such a model would be able to characterise drug effects arising from an interaction at different receptor types, as has been shown for clonidine.[42] The model was the only one to adequately describe the morphine long infusion data (fig. 2). However, the reverse agonist model predictions for the furosemide and morphine long infusion data demonstrated large negative effects. In these cases, the tolerance effect was described by a linear model. To fully characterise the effect, both the reverse agonist model and the partial agonist model use at least 8 parameters, which puts high demands on the design.

The direct moderator model gave a good description of the nicotine data (fig. 1) and the furosemide data (fig. 5), but was less successful with the other data sets. The estimated profiles were sometimes oscillatory, exemplified by the fit to the morphine long infusion data (fig. 2). In the direct moderator model, tolerance reduces the effect in an additive way, while in the indirect moderator model tolerance is incorporated in a multiplicative form. Both models are able to characterise rebound effects, but not necessarily to the same extent as tolerance. The indirect moderator model gave a good fit to the remoxipride data, which originated from an indirect response model (fig. 6). From a practical point of view, the estimations with both the direct moderator model and the indirect moderator model required long running times and were particularly sensitive to initial estimates of parameter values, considerably more so than any of the other models.

The adaptive pool model managed to characterise 4 data sets and performed better than the pool model. Since the different parts of the pool model are sequentially organised, the flexibility of the model is limited. The pool can be physiologically interpreted as storage of a hormone[3] or a transmitter substance,[19] which will be depleted on stimulation by a drug or an endogenous compound resulting in an increased response. The feedback mechanism can be understood as a counter-regulatory homeostatic phenomenon or regulation of cellular processes. The depletion rate is dependent on the stimuli, producing peaks of a larger magnitude and shorter duration when the stimulus intensity increases.[19] Following removal of the stimulus, the rate of change of the pool size is governed by k_{in}, the rate constant of the basal stimulation. Parameter estimates obtained from the pool model can be used for predictions of the response following other doses or input modes. However, inclusion of the feedback function in the adaptive pool model limits the prediction possibilities, unless the feedback function is fully characterised. This was demonstrated in figure 8 (nicotine data set), where the tolerance is reduced at the end of the long infusion due to an increased input rate into the pool. More complex schemes based on the pool model have been presented by Ekblad and Licko.[19]

4.2 Design

All the original experiments of part I were, with the exception of the morphine/morphine-3-glucuronide study, designed to characterise tolerance. The large heterogeneity in design, despite this common aim, indicates that a multitude of considerations need to be made when choosing administration strategies for adaptive systems. Several important factors for study design can be recognised: (i) the absolute and relative time courses of the pharmacokinetics, the concentration-effect delay

and the development of tolerance; (ii) the extent of tolerance development; (iii) the expected tolerance mechanism; and (iv) practical constraints. In addition, optimal study design depends somewhat on whether the objective of the study is model discrimination, parameter estimation, characterisation of a particular process component or predictions of envisaged dosage schemes in the future. Here, some general observations regarding study design will be made.

4.2.1 Design Strategies

Three principal design strategies can be distinguished for characterising systems demonstrating tolerance:

(i) continuous exposure

(ii) rechallenging, by reintroducing or changing the drug exposure at different levels of tolerance development

(iii) deduction of tolerance from the joint analysis of different designs.

(i) In a continuous infusion design, it is of importance that the exposure is long enough to ensure that sufficient tolerance has developed at that particular concentration. In the morphine long infusion and the morphine/morphine-3-glucuronide studies, the study time was short in relation to the estimated tolerance development, which contributed to the unreliable estimates of tolerance and disparate predictions between the 2 models. If possible, it is advisable to follow the effect until a stable baseline is attained. In addition to the duration of exposure, it is of importance to assess tolerance at different concentration (or effect) levels, as was done within the morphine long infusion data.

(ii) In a rechallenging design, it is important that the consecutive doses are administered at different levels of tolerance either during the development of tolerance (as in the alfentanil experiment) or during diminution of tolerance (as in the remoxipride experiment). In order to follow the diminution, the initial dose should ideally give maximal or near-maximal tolerance (the nicotine and remoxipride designs); to follow the increase in tolerance, each concentration level should develop tolerance to a large extent (the alfentanil design). In addition, a stepwise infusion of a length not inconsiderable compared with the time of tolerance development allows a separation of rate and extent of tolerance. The models selected for part II from these data sets demonstrated matching predictions, indicating a well-characterised tolerance. In contrast, the part II furosemide predictions showed a large disparity between the models, although tolerance was challenged by repetitive doses. However, relative to the tolerance half-life (7 hours), the study duration was short (14 hours). In both the remoxipride and the nicotine experiments, rechallenging was carried out at different times after the first exposure, but with the same dose at each time. This provides a good description of the time course of tolerance. Instead of administering equal doses, a design consisting of differently sized doses could also be imagined. Such a design, not explored in this study, might provide more information regarding the extent of tolerance, but might be less successful in determining the tolerance rate.

(iii) All studies, with exception of the furosemide study, rely on the joint analysis of data from separate experiments with different designs, even when one or more of the separate experiments is designed as continuous infusions or has a rechallenging component. Although this provides rich information about the system, it assumes that inter-individual or inter-occasion variability is handled in a manner that does not invalidate the result. With the furosemide and morphine/morphine-3-glucuronide experiments as the only exceptions, the original analysis pooled data across the individuals or study occasions without recognising potential variability in parameters. Although pooling of data has shown to provide useful descriptions of simple systems,[43] such results cannot necessarily be extrapolated to these complex and often quite nonlinear systems.

Whatever the choice of design, a reliable estimation of the baseline is important to account for variation over time, because of such factors as a habituation process or circadian variations. Several physiological processes, such as hormone se-

cretion and haemodynamic variables, are subjected to chronotropic variations and for some drugs such variations have been incorporated in the pharmacodynamic evaluation.[16,29,44]

4.2.2 Relative Kinetics of Drug, Effect and Tolerance

Irrespective of study design, the relative kinetics of the drug, the effect and the development of tolerance have to be considered. The tolerance process will not be detected unless it develops at a slower rate than that of the effect. Furthermore, slow drug kinetics in relation to the rate of tolerance development will reduce the extent of rebound effects, since the tolerance-mediating system will have time to adjust itself. The interaction between relative rates and study design is complex, but some general notions can be outlined.

Slow tolerance development relative to the effect indicates that drug exposure has to be prolonged to ensure that tolerance develops. This might lead to practical difficulties when using a rechallenging design, since it implies that the interdose intervals and drug infusions have to be long and that rebound effects might develop within the administration intervals. On the contrary, in a situation where development of tolerance is rapid relative to, or even similar to, drug elimination, the diminution of tolerance can be followed by rechallenging the system at various time points. When tolerance develops at a much slower rate compared with the effect, the 2 phenomena can be readily separated by, for example, a step-infusion regimen, although a slowly developing effect and a consequently slow development of tolerance might be difficult to separate.[11]

The length of the drug exposure in part II was chosen relative to the rate of tolerance development for all data sets. The significance of considering the relative rates is exemplified by alfentanil, which has an elimination half-life of the same length as the tolerance half-lives estimated by the tolerance compartment models. Thus, prediction of alfentanil effects during a long infusion, as shown in figure 8, demonstrates that the development of tolerance was masked by the increasing drug concentrations and would probably be difficult to quantify. On the contrary, in the stepwise infusion or the consecutive infusion designs, tolerance was clearly observed.

4.2.3 Input Rate

It has previously been shown that the input rate has a profound influence on development of tolerance for several drugs.[1] When the effect of nicotine on heart rate was compared between cigarettes and nicotine gums, the slower input rate of the gum allowed tolerance to develop during the input, resulting in lower effects of the gum.[45] In another study, morphine was administered at 3 infusion rates for 10 minutes, 1 or 3 hours. For the shortest infusion an anticlockwise hysteresis loop was evident from the plasma concentration-effect data, while the longest infusion gave a pronounced clockwise hysteresis.[14] From the intermediate infusion rate no hysteresis was observed, indicating the influence of the administration rate on the detectability of tolerance. For organic nitrates, intermittent drug administration was recommended in preference to a continuous regimen, because of the higher degree of tolerance in the latter case.[46]

For drugs whose response triggers homeostatic compensatory mechanisms, the administration rate has been shown to be an important determinant of development of tolerance. A well-known example is the hypotensive effect of nifedipine, which is more pronounced during slow administration due to the capability of the baroreceptor reflexes to adjust themselves.[47] Thus, contrary to the nicotine example, a slower input of nifedipine results in larger effects. Similar conclusions were also drawn for the hypotensive response of prazosin.[1]

4.3 Data Evaluation

As expected, the alternative models display the same or higher objective function value than the original model (table VI). Based on the magnitude of the differences, the data sets could be divided into 3 groups, demonstrating large (remoxipride and alfentanil), intermediate (morphine long infusion and morphine short infusion) and small (furosemide, nicotine and morphine/morphine-3-

glucuronide) differences between the original and the alternative models. These differences are dependent on the amount of data and the capacity of the alternative model to mimic the profile from the original model. The latter will depend on the design of the study and also on the mechanism for and the extent of tolerance development. The data sets showing the large differences originated from well-designed studies with a large amount of observations.

Among the data sets showing small differences between the original and the alternative models, the furosemide data exhibited a low extent of tolerance and the design of the morphine/morphine-3-glucuronide data was not informative, which could explain the small differences for these data sets. The nicotine data exhibited a considerable extent of tolerance and the study was informative, as demonstrated by the reliable predictions (fig. 8). An explanation for the low difference in the objective function value may be that the noncompetitive antagonist model used for the original data set is relatively easy for the other, more complex, models to mimic.

One objective of this study was to make suggestions regarding the model selection process when tolerance is modelled empirically. The experimental design and the extent and mechanism of tolerance are both factors that will have an impact on the model selection process. Generally, if the data express tolerance to a low extent, different types of models will describe the data well, as exemplified by the furosemide data. Only a few models will fit to data characterised by extensive tolerance, for example for remoxipride, due to the more extensive information about the properties of the tolerance. Moreover, since the prolactin response to remoxipride demonstrated rebound effects, the number of appropriate models was reduced. Generally, an informative design will ensure that any model offering a good fit to the data will result in reasonable predictions, exemplified by the part II predictions for alfentanil, nicotine and remoxipride, while the reverse is observed for an uninformative design [e.g. the data for morphine (long infusion) and morphine/morphine-3-glucuronide].

5. Conclusions

There appears to be little reason to promote one type of empirical tolerance model over the others, or to discourage the use of any of the discussed models. Rather, it would seem to be good practice to avoid trying only 1 or 2 types of models, as is commonplace today, and instead use a range of models. Likewise, it can be recommended that the predictive performance of the models that acceptably describe data is evaluated. If the models then perform similarly, the choice of model will be arbitrary. However, if the models display disparate predictions, this indicates that the system is not well characterised and that all models will have limited predictive value.

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