Pharmocokinetic-pharmacodynamic model for educational simulations

Pharmacokinetic-Pharmacodynamic Model for Educational Simulations

Willem L. van Meurs,* *Member, IEEE*, Eric Nikkelen, and Michael L. Good

***Abstract*— Pharmacokinetic-pharmacodynamic (PK-PD) models play an important role in educational simulations. The parameters of PK-PD models described in the scientific literature are obtained from studies in which the drug concentrations and the drug-effect data are measured simultaneously. Simultaneous PK-PD studies cannot be expected to incorporate all possible combinations of drugs and patient physiology that are desired for educational simulations. To solve this problem, we elaborate on the traditional simultaneous PK-PD model, creating a new model that accepts parameter data from different, more readily available, nonsimultaneous pharmacologic studies. These data are incorporated in the model using a novel estimation procedure for the parameters k_{e0} and EC_{50}. A sensitivity analysis of the parameter estimation procedure confirms that the time of peak effect following a bolus and the dose-response curve are accurately reflected by the new model. It also demonstrates how inconsistencies among the different parameter sets affect simulation of the recovery phase. The model is extended to incorporate any monotonic parametric or nonparametric dose-response curve. For the neuromuscular relaxant vecuronium, we demonstrate that data from different pharmacologic studies are available, and that the described estimation procedure leads to parameter estimates that are within the standard deviations of the parameters determined in a simultaneous PK-PD study.**

***Index Terms*— Educational simulation, mathematical model, parameter estimation, pharmacodynamics, pharmacokinetics, sensitivity analysis.**

I. Introduction

SIMULATIONS developed for the education and training of health care professionals typically use computerized mathematical models of human physiology and pharmacology as their "simulation engine" [1], [2]. To determine the simulated patient's response (output) to a bolus injection or continuous infusion of a drug (input), the equations must account for both pharmacokinetic effects (PK) (drug uptake, distribution, and elimination) and pharmacodynamic effects (PD) (relationship between the drug concentration at the effector site and the measured clinical effect). The most commonly used approach to simultaneous PK-PD modeling is based on the work of Hull *et al.* [3] and Sheiner *et al.* [4].

Unlike theoretical or therapy-directed simulations [5], [6], [7], educational simulations typically involve many drugs, multiple clinical effects and, therefore, multiple effector sites for each drug, and a variety of patient groups. Unfortunately, developers of educational simulations find that simultaneous PK-PD studies and data sets are available for only a limited number of drugs, effector sites, and patient groups. In this paper, we present a new approach to simultaneous PK-PD modeling for the purpose of educational simulations, which allows model parameters to be acquired from separate PK and PD studies and data sets.

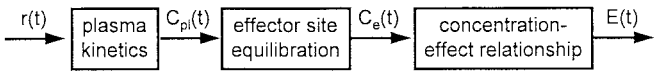

Fig. 1. Block diagram of a traditional simultaneous pharmacokinetic-pharmacodynamic model: $r(t)$ is the infusion rate, $c_{\rm pl}(t)$ is the plasma concentration, $c_e(t)$ is the effector site concentration, and $E(t)$ is the effect, as a function of time t.

A. Description of the Traditional Simultaneous PK-PD Model

The time profile of blood plasma concentration following a bolus dose (D) of an intravenous drug can often be approximated by a sum of exponentials with different disposition rate constants (λ_i) and relative amplitudes (A_i) [8]

$$c_{\rm pl}(t) \cong \frac{D}{V_1}\sum_{i=1}^{n} A_i e^{-\lambda_i t}, \quad \sum_{i=1}^{n} A_i = 1 \tag{1}$$

where $c_{\rm pl}(t)$ is the plasma concentration at time t. The initial plasma concentration is equal to the administered dose (D) divided by the initial volume of distribution (V_1); n is the order of the kinetics and typically equals two or three.

The plasma kinetics can be combined with drug distribution to a hypothetical effector compartment, and with a relationship between the apparent concentration at the effector site $c_e(t)$ and the measured or observed clinical effect [3]–[5], (Fig. 1). The amount of drug distributed to the effector compartment is assumed to be so small that it can be ignored in the mass balance of the drug in the plasma.

The equilibration of the plasma concentration and the effector site concentration is typically described by a unity gain

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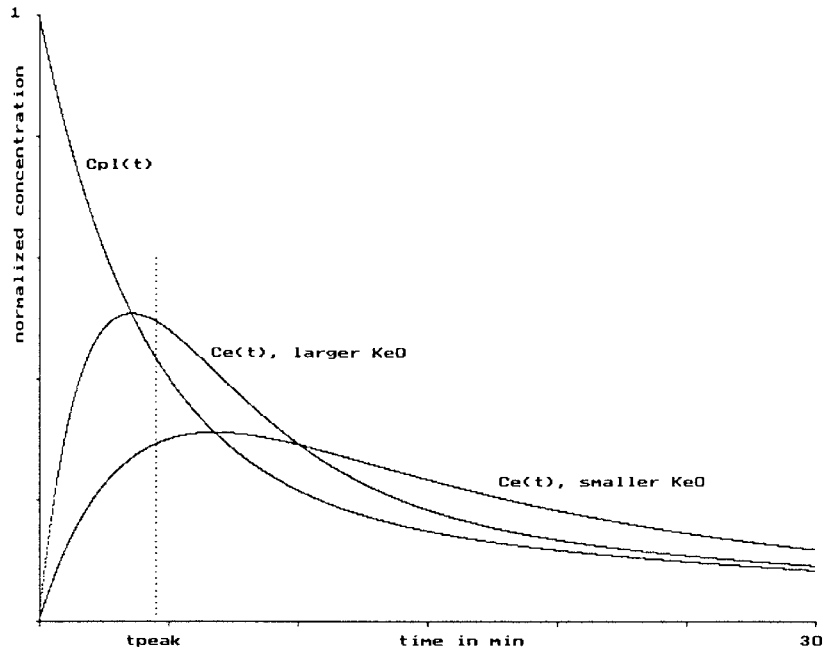

Fig. 2. Plasma concentration $c_{\rm pl}(t)$ and effector site concentration $c_e(t)$ as a function of time for two different values of the parameter k_{e0}. The concentrations are normalized to an initial plasma concentration of one. For later use, we also indicate a specific time of peak effect: $t_{\rm peak}$.

first-order differential equation [4], [5], [7], [9]

$$\frac{dc_e(t)}{dt} = k_{e0}\{c_{\rm pl}(t) - c_e(t)\}. \tag{2}$$

The inverse time constant k_{e0} is the parameter determining the equilibration. Fig. 2 shows a simultaneous plot of $c_{\rm pl}(t)$ and $c_e(t)$ for two values of k_{e0}.

The PD relationship between the effector site concentration $c_e(t)$ and the effect $E(t)$ can be represented by the following parametric relationship [10]:

$$E(t) = E_0 + (E_{\max} - E_0)\frac{c_e(t)^\gamma}{c_e(t)^\gamma + EC_{50}^\gamma} \tag{3}$$

where E_0 is the effect when no drug is present, $E_{\max}$ is the maximum possible effect caused by the drug, EC_{50} is the effector site concentration associated with an effect halfway the difference between $E_{\max}$ and E_0, and γ is the Hill coefficient that determines the steepness of the relationship.

II. Methods

We first show that the parameters of the presented traditional simultaneous PK-PD model can be derived from three independent, more readily available, nonsimultaneous, parameter sets. These sets are: pharmacokinetic data, the time of peak effect, and the dose-response curve, respectively. We introduce methods for estimating the parameters k_{e0} and EC_{50}, based on these sets. We then present a sensitivity analysis to evaluate how errors and inconsistencies in the three separate sets influence the derived parameters and the model response. Finally, we introduce a modification to this model, that allows for the incorporation of any monotonic dose-response curve.

A. Pharmacokinetic Parameter Estimation

Published PK parameters govern the relationship between drug administration and the resulting time profile of blood plasma concentration. The PK part of the simultaneous PK-PD model (1) describes the exact same phenomenon, and, therefore, its parameters V_1, λ_i, and A_i, are directly taken from independent PK data. For most of the intravenous drugs routinely used in anesthetic practice and acute care medicine, and for a wide variety of patients, these parameters can be readily obtained from the scientific literature on pharmacokinetics.

B. k_{e0} Estimation

The parameter k_{e0} (2) is usually estimated with a procedure that is based on minimization of the hysteresis between a predicted effector site concentration and the effect [4], [11]. This requires the plasma concentration and the effect to be measured simultaneously, which is done in only a limited number of published studies. We observe that if the PD relationship (3) is monotonic, then the peak of the effector compartment concentration following a bolus dose will coincide with a unique extreme (either maximum or minimum) of the effect. For the time of peak effect data, only bolus dosages that do not saturate the effector characteristic should be taken into account. For saturating dosages, the peak effect occurs *before* the effector compartment concentration reaches its peak. Often, data are available on the time of peak effect $(t_{\rm peak})$ following a bolus administration, for example, in the form of heart rate over time, twitch height depression over time, etc. Given λ_i, A_i, and V_1, the only "degree of freedom" in the model that is left to determine the time of peak effect is the parameter k_{e0} (Fig. 2).

By taking the Laplace transform of $c_{\rm pl}(t)$ (1), multiplying it with the Laplace transform of (2), and taking the inverse

transform of the result, we obtain the following expression for the effector site concentration following a bolus of magnitude D:

$$c_e(t) = \frac{Dk_{e0}}{V_1}\left\{\sum_{i=1}^{n}\frac{A_i}{\lambda_i - k_{e0}}(e^{-k_{e0}t} - e^{-\lambda_i t})\right\}. \quad (4)$$

If the equilibration parameter k_{e0} is equal to λ_j, one of the disposition rate constants λ_i, then the expression for the effector site concentration becomes

$$c_e(t) = \frac{Dk_{e0}}{V_1}\left\{A_j t e^{-\lambda_j t} + \sum_{i=1, i\neq j}^{n}\frac{A_i}{\lambda_i - k_{e0}} \times (e^{-k_{e0}t} - e^{-\lambda_i t})\right\}. \quad (5)$$

Our goal is to find a $\hat{k}_{e0}$ that results in a maximum of $c_e(t, \hat{k}_{e0})$ in t_{peak}. Taking into account (2), we note that the plasma concentration and the effector site concentration at t_{peak} are identical. An equivalent formulation of our goal is, therefore, to find a $\hat{k}_{e0}$ that results in

$$c_e(t_{\text{peak}}, \hat{k}_{e0}) = c_{\text{pl}}(t_{\text{peak}}). \quad (6)$$

Looking at (1), (4), and (6), we observe that there is no known analytical solution for the relationship between $\hat{k}_{e0}$ and t_{peak}. We, therefore, need to find $\hat{k}_{e0}$ using an iterative method. We define the following function of the parameter estimate $\hat{k}_{e0}$:

$$F(\hat{k}_{e0}) = c_e(t_{\text{peak}}, \hat{k}_{e0}) - c_{\text{pl}}(t_{\text{peak}}). \quad (7)$$

Let k_{e0} be the parameter that leads to a maximum of the effector site concentration in t_{peak}. Observing Fig. 2, we see that $F(\hat{k}_{e0})$ is a continuous function of $\hat{k}_{e0}$, and that $\hat{k}_{e0} = k_{e0}$ is the only root of this function. To find the root, we use the bisection method because of its guaranteed convergence [12]. The stop criterion for the bisection method is that two successive estimates of $\hat{k}_{e0}$: $\hat{k}_{e0}(m)$ and $\hat{k}_{e0}(m+1)$ lie within a distance ε of each other

$$|\hat{k}_{e0}(m+1) - \hat{k}_{e0}(m)| < \varepsilon. \quad (8)$$

This guarantees the following limit on the estimation error:

$$|\hat{k}_{e0}(m+1) - k_{e0}| < \varepsilon/2. \quad (9)$$

To obtain $F(\hat{k}_{e0})$, we use (1) to compute $c_{\text{pl}}(t_{\text{peak}})$ and (4) to compute $c_e(t_{\text{peak}}, \hat{k}_{e0})$. Equation (4) has a singularity if $\hat{k}_{e0}$ is equal to one of the disposition rate constants λ_j. Therefore, in small intervals δ around $\hat{k}_{e0} = \lambda_j$, we replace $c_e(t_{\text{peak}}, \hat{k}_{e0})$ by $c_e(t_{\text{peak}}, \lambda_j)$, computed using (5). This procedure results in a discontinuous, but bounded function $F(\hat{k}_{e0})$, not affecting the convergence properties of the bisection method, provided δ is small compared to ε. For our educational simulation application, we use $\varepsilon = 0.001$ min^{-1}, and $\delta = 0.0001$ min^{-1}. All simulations presented in this paper were carried out on a Pentium-based personal computer, using software written in Borland® (Borland International, Inc.).

C. Pharmacodynamic Parameter Estimation

The traditional dose-response curve [13] gives the relationship between a bolus dose D and the peak effect caused by it. From this curve, E_0 and $E_{\max}$ of the PD relationship between the apparent effector compartment concentration $c_e(t)$ and the effect $E(t)$ (3) can be derived directly. The other two parameters of this relationship, EC_{50} and γ, are only estimated in simultaneous PK-PD studies. We will show how these parameters can be derived from parameters obtained from other, more readily available sources.

The system given by (1) and (2) is a linear system and, therefore, $c_e(t_{\text{peak}})$ is proportional to the dose D. We noted earlier (6) that $c_e(t_{\text{peak}}) = c_{\text{pl}}(t_{\text{peak}})$. Using this result and (1), we find the proportionality constant K_n

$$K_n = \frac{D}{c_e(t_{\text{peak}})} = \frac{D}{c_{\text{pl}}(t_{\text{peak}})} = \frac{V_1}{\sum_{i=1}^{n} A_i e^{-\lambda_i t_{\text{peak}}}}. \quad (10)$$

EC_{50} is related to the dose ED_{50} resulting in an effect halfway between E_0 and $E_{\max}$, by the same proportionality constant

$$EC_{50} = \frac{ED_{50}}{K_n}. \quad (11)$$

ED_{50} is directly read from the dose-response curve. K_n is computed using (10), based on PK data, and the time of peak effect. $\hat{EC}_{50}$, the estimated EC_{50} for our educational application, is computed using (11).

Another consequence of the linearity of the system represented by (1) and (2) is that the Hill coefficient γ, which determines the steepness of the pharmacodynamic relationship, is identical to the Hill coefficient of the dose-response curve. This can be derived formally by substituting $c_e(t_{\text{peak}}) = D/K_n$ and $EC_{50} = ED_{50}/K_n$ in (3). Dose-response curve data for many drugs and patient groups are available in the literature, and the parameters ED_{50} and γ can be derived from there.

D. Sensitivity Analysis

Sections II-A–II-C describe how we derive the parameters of a traditional simultaneous PK-PD model from three independent, more readily available, nonsimultaneous, parameter sets. We carry out a sensitivity analysis to answer the following questions: "How do errors or inconsistencies in these independent sets affect the parameter estimates, and how do these errors influence the model output?" The type of inconsistencies that can occur when selecting different data sets are: differences in patient characteristics, experimental setup, and measured effect.

The model parameters V_1, A_i, λ_i, and γ are derived directly from identical parameters in one of the independent sets. Relative errors in these parameters therefore have unit sensitivity to relative errors in the original parameters. The influence of errors in V_1, A_i, $\lambda_i, t_{\text{peak}}$, ED_{50}, and γ on the parameter estimates $\hat{k}_{e0}$ and $\hat{EC}_{50}$ is investigated more in depth. The PK parameters that are taken from the dose-response curve: ED_{50} and γ do not affect the estimation of $\hat{k}_{e0}$. Therefore, errors in these parameters do not lead to errors in $\hat{k}_{e0}$. From (10) and (11), it can be observed that errors in γ have no effect on

errors in $\hat{E}C_{50}$, and that relative errors in ED_{50} propagate with unit sensitivity to relative errors in $\hat{E}C_{50}$. V_1 is a multiplicative term in (1), (4), and (5), and has no effect on the root of the minimized function $F(\hat{k}_{e0})$ (7). Therefore, errors in V_1 do not lead to errors in $\hat{k}_{e0}$. From (10) and (11), it can be observed that relative errors in V_1 propagate with unit sensitivity to relative errors in $\hat{E}C_{50}$.

No known analytical expression exists for $\hat{k}_{e0}$ as a function of the parameters of the independent sets. Therefore, we determine the influence of errors in the remaining parameters (A_i, λ_i, and t_{peak}) from the independent sets experimentally, and for a specific set of independent parameters. Although error propagation to $\hat{E}C_{50}$ can be determined analytically based on (10) and (11), we determine the influence of errors in the remaining parameters on errors in $\hat{E}C_{50}$ and $\hat{k}_{e0}$ experimentally in identical conditions. This facilitates comparison of the sensitivity to error of both estimates.

A set of simultaneous PK-PD parameters for the effect of the intermediate acting neuromuscular blocking agent vecuronium on single twitch force depression (STFD) is given in Table I [14]. We first determine the three nominal independent sets associated to this simultaneous set. The pharmacokinetic parameters are directly taken from Table I. The time of peak effect t_{peak}, corresponding to the nominal parameters of Table I, was determined by searching the maximum of $c_e(t)$ (3), and found to be equal to 4.55 min. Using (10), the normalization constant K_n, associated to the nominal set of Table I, is found to be equal to 0.178 l/kg, resulting in the PD parameter $ED_{50} = 0.0244$ mg/kg (11). The other PD parameter, γ, is directly taken from Table I.

For each of the parameters A_1/A_2, λ_1, λ_2, and t_{peak} of the independent sets, $\hat{k}_{e0}$ and $\hat{E}C_{50}$ are determined, using the methods described in Section II-A–II-C, for 75% and 125% of the nominal parameter values.

The second question that we address by a sensitivity analysis is: "How do errors or inconsistencies in the independent sets affect the model output?" We noted above that V_1 has no influence on $\hat{k}_{e0}$. Combining this observation and the result of the substitution of (11) in (10), and of (10) in (3), we see that—as a result of the normalization of the $c_e(t)$ on the administered dose—V_1 has no influence on the response. Again, because no known analytical expression exists for $\hat{k}_{e0}$ as a function of the other parameters of the independent sets, we use an experimental approach in which we vary one of the independent parameters at a time, and evaluate the effect on the overall model response. The simulated response is one to a dose of 0.041 mg/kg, which is the ED_{95} corresponding to the parameters of Table I. For each of the parameters $A_1/A_2, \lambda_1, \lambda_2$, t_{peak}, ED_{50}, and γ, $\hat{k}_{e0}$ and $\hat{E}C_{50}$ are determined using the methods described in Section II-A–II-C, for 75% and 125% of the nominal parameter values. The model response is computed using (3) and (4).

E. Vecuronium Parameter Data

The feasibility of acquiring parameter data is demonstrated by an example using the neuromuscular relaxant vecuronium. Above, we presented a set of parameters reported in a simultaneous PK-PD study, Table I. We show that these parameters can also be derived from three independent sets of data, using the described parameter estimation procedures.

TABLE I
SIMULTANEOUS PK-PD DATA FOR VECURONIUM [14]. DATA ARE REPORTED AS MEAN ± STANDARD DEVIATION. THE DISPOSITION RATE CONSTANTS λ_1 AND λ_2 ARE REPORTED IN THE REFERENCE AS α AND β, RESPECTIVELY. THE AMPLITUDES A AND B ARE NORMALIZED TO YIELD THE PARAMETERS A_i, WITH A SUM OF ONE. ONLY MEANS ARE REPORTED FOR THESE PARAMETERS. THE PD PARAMETERS E_0 AND $E_{\max}$ FOLLOW FROM THE MINIMUM AND MAXIMUM STFD OF THE ADDUCTOR POLLICIS MUSCLE, RESPECTIVELY

Reported parameters		Derived parameters	
λ_1 [min^{-1}]	0.25 ± 0.15		
λ_2 [min^{-1}]	0.03 ± 0.018		
A [μg/ml]	1.214 ± 0.732	A_1	0.798
B [μg/ml]	0.308 ± 0.133	A_2	0.202
V_1 [l/kg]	0.077 ± 0.029		
k_{e0} [min^{-1}]	0.27 ± 0.07		
E_0 [%stfd]	0		
E_{max} [%stfd]	100		
EC_{50} [μg/ml]	0.137 ± 0.027		
γ	5.7 ± 1.5		

F. Description of the New Model

The model has to respond to a multitude of dosing schemes (boluses and infusions). We, therefore, compute the plasma concentration by numerical integration of the following continuous state variable equation, for $n = 3$

$$\frac{dx(t)}{dt} = \begin{bmatrix} -\lambda_1 & 0 & 0 \\ 0 & -\lambda_2 & 0 \\ 0 & 0 & -\lambda_3 \end{bmatrix} x(t) + \begin{bmatrix} 1 \\ 1 \\ 1 \end{bmatrix} r(t) \quad (12)$$

$$c_{\mathrm{pl}}(t) = \frac{1}{V_1}[A_1 \quad A_2 \quad A_3]x(t) \quad (13)$$

where $r(t)$ is the infusion rate as a function of time and $x(t)$ is a vector of state variables. If we set $r(t) = D\delta(t)$, where $\delta(t)$ is the unit Dirac function, then each state variable represents one exponential of (1). For second-order plasma kinetics, A_3 is put to zero. The effector site concentration is computed from the plasma concentration by numerical integration of (2).

In order to express the effect $E(t)$ in terms of a directly measurable dose-response quantity (for example, ED_{50} rather than EC_{50}), we extend the traditional PK-PD model by normalizing $c_e(t)$ so that the peak value of the resulting $c_{e,n}(t)$ is equal to the administered dose

$$c_{e,n}(t) = K_n c_e(t) \quad (14)$$

(Fig. 3). For any drug that exhibits a monotonic dose-response curve, a $\hat{k}_{e0}$ estimate can be computed, based on a given set of PK parameters and a t_{peak}. Based on $c_{e,n}(t)$, this parametric or nonparametric dose-response curve is then directly used to derive the effect.

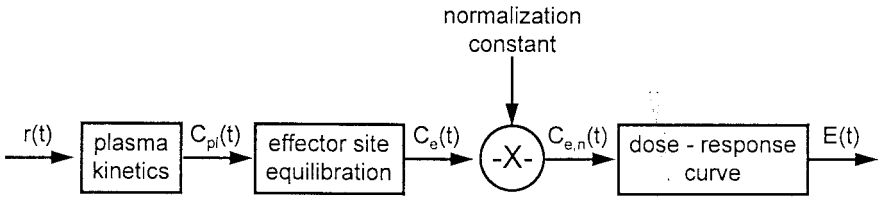

Fig. 3. Block diagram of the new PK-PD model: $r(t)$ is the infusion rate, $c_{\mathrm{p1}}(t)$ is the plasma concentration, $c_e(t)$ is the apparent effector compartment drug concentration, $c_{e,n}(t)$ is the normalized effector site concentration, and $E(t)$ is the effect, as a function of time t.

TABLE II
SENSITIVITY ANALYSIS: ESTIMATES $\hat{k}_{e0}$ AND $\hat{EC}_{50}$ FOR 75%, 100%, AND 125% OF SELECTED NOMINAL INDEPENDENT PARAMETERS FOR VECURONIUM, ASSOCIATED TO THE PARAMETERS GIVEN IN TABLE I

	$\hat{k}_{e0}$ [min^{-1}]	$\hat{EC}_{50}$ [mg/l]
A_1/A_2		
2.96	0.291	0.146
3.95	0.270	0.137
4.94	0.256	0.131
λ_1 [min^{-1}]		
0.188	0.323	0.164
0.250	0.270	0.137
0.313	0.234	0.117
λ_2 [min^{-1}]		
0.0225	0.275	0.139
0.0300	0.270	0.137
0.0375	0.265	0.135
t_{peak} [min]		
3.41	0.438	0.166
4.55	0.270	0.137
5.69	0.184	0.115

III. RESULTS

A. Sensitivity Analysis

Table II gives the estimated parameters $\hat{k}_{e0}$ and $\hat{EC}_{50}$ for 75%, 100%, and 125% of the nominal parameter values.

From the values in Table II, it follows that $\hat{k}_{e0}$ is most sensitive to errors in t_{peak}. This result justifies the use of t_{peak} as a parameter to base a $\hat{k}_{e0}$ estimate on. It also warrants caution when determining t_{peak} experimentally or selecting a t_{peak} data set from the literature; errors or inconsistencies between t_{peak} and the pharmacokinetic data set can lead to significant errors in the $\hat{k}_{e0}$ estimate. All other relative errors in $\hat{k}_{e0}$ and $\hat{EC}_{50}$ have less than unit sensitivity to relative errors in the independent parameter sets. $\hat{k}_{e0}$ and $\hat{EC}_{50}$ are least sensitive to the parameter λ_2.

Fig. 4 gives the model response for 75%, 100%, and 125% of the nominal parameter values. We evaluate the effect on the response in terms of the clinical aspects of the response: onset (time to peak effect), magnitude, and recovery.

Fig. 4 shows that for these nominal parameters and for this dose, the errors in the PK parameters A_1/A_2, λ_1, and λ_2, only have a small effect on the recovery. The onset and magnitude of the response are not affected. Note, that errors in the parameters A_1/A_2 and λ_1 have a more pronounced effect on the recovery, and also have an effect on the magnitude of the response when using the traditional model of (1)–(3). The parameter t_{peak} has the intended effect on the time of peak effect. It has no effect on the magnitude of the response. t_{peak} also has a significant effect on the recovery. Note, that errors in the parameter k_{e0} have a pronounced effect on onset, magnitude, and recovery, when using the traditional model. The effect of errors in the parameters γ and ED_{50} is added for completeness only. Their effect on the response is significant, but no different from corresponding changes caused by γ and EC_{50} in the traditional model.

These results can be interpreted as follows: the $\hat{k}_{e0}$ estimation procedure guarantees that the time of peak effect is very close to the specified t_{peak} and, therefore, not dependent on the two other independent parameter sets. The effect of the normalization constant K_n is that the resulting dose-response curve is governed by the parameters γ and ED_{50}, and not dependent on the two other parameter sets. The presented parameter estimation procedure, therefore, guarantees correct simulation of the specified time of peak effect and the dose-response curve. Both of these aspects of drug response are very important in patient care and, therefore, in educational simulations. It follows from the sensitivity analysis that the recovery depends on all three parameter sets, and most markedly on t_{peak}. If recovery of drug effect is important in a clinical simulation scenario, care has to be taken that the three independent sets are consistent.

B. Vecuronium Parameter Data

Table I gives the parameters for the traditional simultaneous pharmacokinetic-pharmacodynamic model described in the introduction, for the nondepolarizing neuromuscular blocking agent vecuronium [14]. Table III gives the pharmacokinetic parameters for the same drug and a similar patient group, derived from a separate source [15]. These parameters are within the range of standard deviations of the same parameters in Table I.

Table IV gives the time of peak response [16]. $\hat{k}_{e0}$ and K_n are derived from t_{peak}, and from the mean values for the parameters reported in Table III, using the methods described in the parameter estimation sections. $\hat{k}_{e0}$ is within the range of standard deviations of the same parameter in Table I.

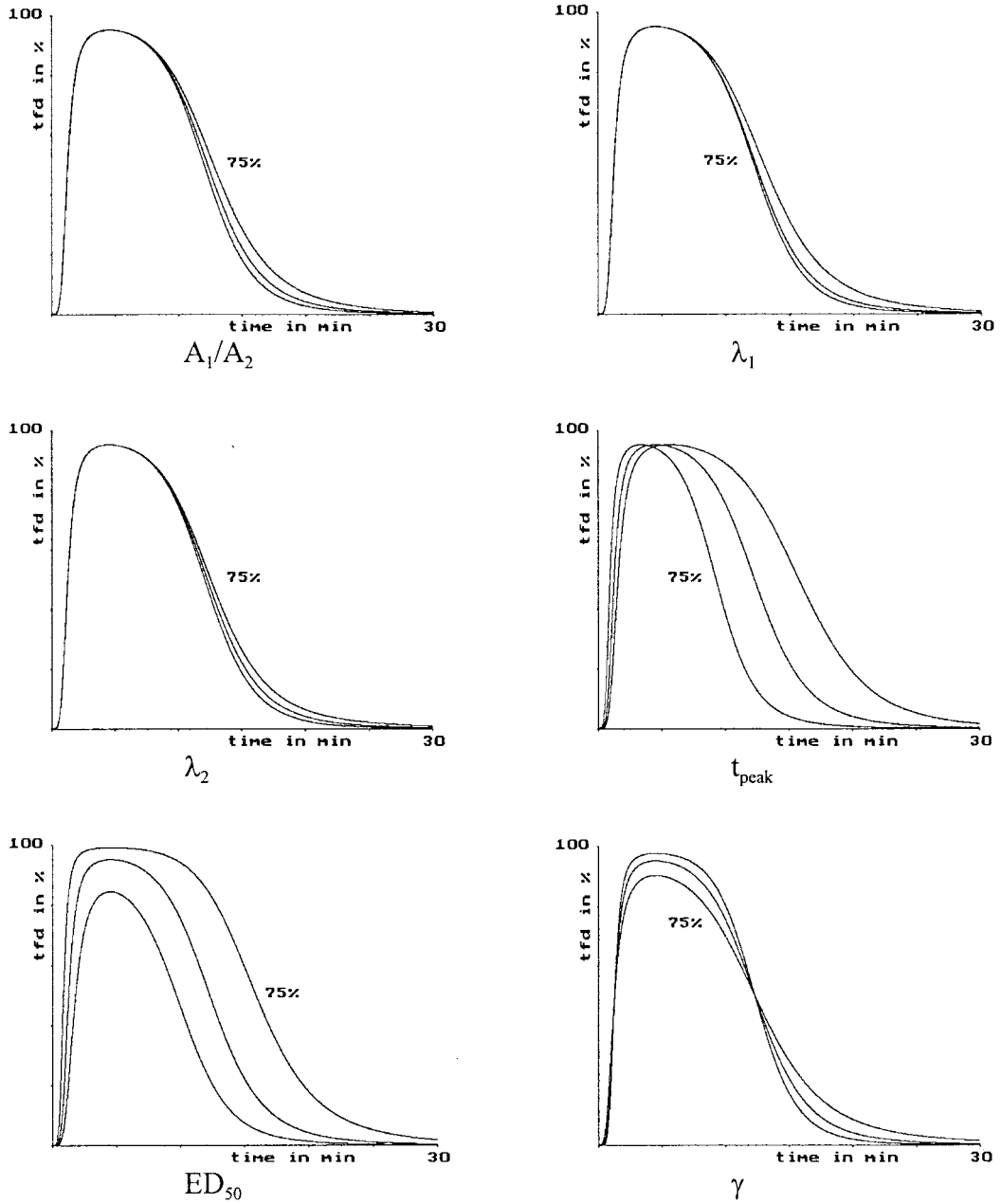

Fig. 4. Sensitivity analysis: Simulated STFD response to a dose of 0.041 mg/kg of vecuronium for 75%, 100%, and 125% of the nominal parameter values.

TABLE III
PK DATA FOR VECURONIUM [15]. DATA ARE REPORTED AS MEAN ± STANDARD DEVIATION. V_1 IS DERIVED BY DIVIDING THE DOSE (0.1 MG/KG) BY THE SUM OF THE AMPLITUDES A AND B

Reported parameters		Derived parameters	
λ_1 [min^{-1}]	0.1729 ± 0.0097		
λ_2 [min^{-1}]	0.0148 ± 0.0011		
A [μg/ml]	1.628 ± 0.128	A_1	0.874
B [μg/ml]	0.235 ± 0.013	A_2	0.126
		V_1 [l/kg]	0.0536

TABLE IV
TIME OF PEAK TWITCH HEIGHT DEPRESSION OF THE FIRST RESPONSE OF A TRAIN OF FOUR AT THE ADDUCTOR POLLICIS FOLLOWING A BOLUS OF VECURONIUM [16], AND DERIVED PARAMETERS. THE REPORTED t_{peak} IS FOR AN ED_{50}. THE DERIVATIONS OF k_{e0} AND K_n ARE DESCRIBED IN THE CORRESPONDING METHOD SECTIONS

Reported parameters		Derived parameter	
t_{peak} [min]	5.93 ± 0.34	k_{e0} [min^{-1}]	0.20
		K_n [l/kg]	0.125

Table V reports the PD parameters that characterize the dose-response curve [17]. The effector site concentration at 50% effect (EC_{50}) is derived from the reported mean value for ED_{50} and from K_n as reported in Table IV, using (11). The steepness parameter (γ) is derived from the mean values for ED_{50} and ED_{95}. Both derived parameters are within the ranges of the standard deviations of the same parameters in Table I.

TABLE V
PD DATA FOR STFD BY VECURONIUM [17]. DATA ARE REPORTED AS MEAN AND 95% CONFIDENCE LIMITS. EC_{50} IS COMPUTED USING (11). γ IS DERIVED FROM ED_{50} AND ED_{95}

Reported parameters		Derived parameters	
ED_{50} [mg/kg]	0.020 (0.017-0.024)	EC_{50} [μg/ml]	0.160
ED_{95} [mg/kg]	0.039 (0.034-0.037)	γ	4.4

We have now shown that all parameters of a traditional simultaneous PK-PD model for vecuronium can be derived using data from three separate sources.

IV. DISCUSSION

Educational simulations require computerized mathematical models of human physiology and pharmacology in order to dynamically generate realistic clinical responses to system perturbations (i.e., pathological events) and to therapeutic interventions (i.e., drug injections or mechanical ventilation of the lungs). Clinicians, scientists, and engineers have collaborated for many years to develop physiologic and pharmacologic models using numerous approaches, and for a variety of purposes. Some of these models are purely theoretical, designed only to enhance scientific understanding of physiologic principles. Many others are designed to automate therapeutic interventions, for example, using target controlled plasma concentration principles to automatically set the delivery of drug from a computer-controlled infusion pump. There are also a number of personal computer-based instruction (CBI) modules that rely on physiologic models. More recently, full-scale human patient simulators have created yet another need for high fidelity, real-time, interactive, and clinically realistic mathematical models of human physiology and pharmacology.

As we began to develop a pharmacology module for a contemporary, state-of-the art Human Patient Simulator (HPS), (Medical Education Technologies, Inc., Sarasota, FL), it quickly became apparent that data sets of simultaneously measured PK and PD data, which provide necessary parameters for the pharmacology model, are often incomplete or simply not available in the published scientific literature. Historically, most pharmacology studies and modeling efforts address either PK's or PD's independently. Much less common are studies or models that examine both PK's and PD's simultaneously. When both PK and PD are considered, the simultaneous PK-PD approach based on the work of Hull *et al*. and Sheiner *et al*. is typically used [3], [4]. In order to derive the necessary model parameters, developers must find or conduct clinical studies, which, in one setting and with one patient population, simultaneously derive both PK and PD parameters. Although there are increasing numbers of this type of study found in the published scientific literature, simultaneous PK-PD studies have not, and cannot be expected to incorporate all possible combinations of drugs and patient groups.

The modeling requirements for educational simulations are less stringent than those for models used to control therapeutic devices, for example, an intravenous drug infusion pump. To control the delivery of drug from an infusion pump for a specific patient, the physiologic and pharmacologic models must accurately predict the behavior of that *specific patient*. In an educational context, the physiologic and pharmacologic models must only describe the behavior of a *plausible patient* belonging to a particular population. A patient population is characterized by demographic and physiologic parameters. Because of the variability seen between different patients, even in the same population, modeling a plausible patient is less complex than modeling a specific patient.

Traditional PK (uptake, distribution, and elimination) parameters and their dependency on age, weight, gender, and especially underlying disease states, are readily available in the published scientific literature. Similarly available, though from different (nonsimultaneous) studies, are PD (dose-response) data for many different patient groups. Thus, it was necessary for us to develop a simultaneous PK-PD model for HPS's and other educational simulations, using a method for acquiring model parameters from separate PK and PD studies and data sets when simultaneous PK-PD data were incomplete or not available. The data on plasma kinetics and the dose response curve are combined with the time to peak clinical effect following a bolus intravenous administration, to generate a complete parameter set for the new model. The mathematical solution, and specifically, the parameter estimation procedure, are the subject of this paper.

Those who develop educational simulations using our approach must recognize the limitations of this method. First, the pharmacokinetic model presented in this paper assumes instantaneous mixing of drug in blood, even though the average recirculation time of blood in man is approximately 1 min. A model that takes into account the recirculation time has been published in the scientific literature [18]. However, the relatively numerous parameters of this model are not available for all drugs and patient groups, making it less suitable for educational simulations. Second, the time of peak effect is used to derive the equilibration time constant for the effector compartment. This is a one data point estimate for application in educational simulations. It does not allow for an estimation of the variability of the k_{e0} obtained in this manner. Therefore, this method is not presented as an alternative for the estimation of k_{e0} based on multiple plasma concentration and effect measurements in a simultaneous study. Third, specific data on the time to peak clinical effect following a bolus intravenous administration is not always available for each drug in each patient population. If the equilibration time constant is known for one group of patients, and for a different group of patients it is assumed not to change, then the presented approach can still be used to complete the parameter set (including the ones determining the plasma kinetics and the dose-response curve) for this second group of patients. Fourth, as underlined by the sensitivity analysis, caution must be used in combining data sets from drastically different patient populations. It is important to maintain consistency in terms of patient groups and underlying pathological conditions for all separate data sets. For example, combining PK data from a group of young, awake, healthy adult volunteers with PD data from a group of geriatric patients receiving general anesthesia while

undergoing coronary artery bypass surgery, produces clinical responses that might mimic neither group. Clearly, each group has unique PK's. The sensitivity analysis demonstrates that the recovery of drug effect is most affected by errors or inconsistencies in the separate data sets. We do note that there is a significant patient variability in recovery time. For the neuromuscular relaxant vecuronium, Wright *et al*. [19] report a 75% recovery time to a $1.2 * ED_{95}$ dose of vecuronium of 26.3 $\pm$6.3 min. Fifth, it is important to maintain consistency between the time of peak effect data and the dose-response data as far as the effector site is concerned. For example, in the case of neuromuscular relaxants, the clinical effects on thumb twitch height depression and on the laryngeal muscles are governed by drug concentrations at different effector sites. These drug concentrations have different time courses. Sixth, it is important to maintain consistency between the intended simulated effect and the measurement method used in obtaining the dose-response data. Elaborating on the neuromuscular relaxant example, measurement of clinical effect using twitch height depression and electromyography will lead to different dose-response curves, even though the effector sites are the same. These last two potential limitations are also a strength of the presented method (and indeed of all simultaneous PK-PD methods): different effector sites can be defined for a single drug with the same set of underlying PK data. In the case of neuromuscular relaxants, there are clinical differences in the effects on the adductor pollicis muscle (responsible for the twitch response to peripheral nerve stimulation), the diaphragm, and the muscles of larynx. Equilibration times between plasma and effector site, and drug sensitivities, are known to be different among these sites [20]. Application of the presented method to different drugs, effector sites, and patient groups will help clarify some of the above raised issues.

V. Conclusion

We elaborated on a traditional simultaneous PK-PD model, to create a new model that accepts parameters from independent, more readily available sources in the literature, using innovative parameter estimation procedure for the parameters k_{e0} and EC_{50}. We have presented a sensitivity analysis of the parameter estimation procedure for the intermediate acting neuromuscular relaxant vecuronium. The analysis confirms that the time of peak effect and the dose-response curve are accurately reflected by the new model. It also indicates how errors and inconsistencies in the independent parameter sets influence the k_{e0} and EC_{50} estimates and the model response, most notably the recovery of drug effect. We have also demonstrated that independent parameters for vecuronium can be obtained from different (non simultaneous) sources, and that the parameters of a traditional simultaneous model can be derived using these data. The new model and associated parameter estimation procedure allow for reliable, data based, educational simulations of drug responses for a wide variety of drugs, drug effector sites, and patient groups, even if simultaneous data are not directly available. The presented approach is successfully applied in the pharmacology module of a full-scale HPS, that calculates responses to more than 55 intravenous drugs.

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