Validation of a Variable Direction Hysteresis Minimization Pharmacodynamic Approach: Cardiovascular Effects of Alfentanil

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An important goal in therapeutics is the quantitative prediction of drug effects. Although several comprehensive pharmacodynamic models have been proposed, relatively few of these have attempted to assess objectively the application of the models to predict pharmacologic responses. A variable-direction hysteresis minimization approach was proposed recently that allowed the pharmacodynamics of drugs to be modeled using information about drug input. The application and validation of this approach are demonstrated using the pharmacodynamic effect of alfentanil, a short-acting narcotic analgesic agent, in New Zealand White rabbits. A parameter is proposed to assess the ability of the pharmacodynamic model to predict responses.

KEY WORDS: alfentanil; heart rate; hysteresis minimization; pharmacodynamic model; system analysis.

INTRODUCTION

An important component of therapeutics is the quantitative prediction of drug effects. Numerous pharmacodynamic approaches have been proposed to elucidate concentration–effect relationships of various drugs. The approaches used have ranged from highly structured effect compartment models where a specific parametric representation is assumed for the concentration–effect relationship (1,2) to more general system analysis approaches where a specific representation of the concentration–effect relationship is not necessary (3,4). Objective assessments of the pharmacodynamic approaches to predict drug responses quantitatively have not been widely published. Recently, a variable direction hysteresis minimization algorithm was proposed for generalized pharmacodynamic modeling (4). In addition to traditional pharmacodynamic modeling, the approach also proposed pharmacodynamic modeling in situations where drug concentrations were unavailable and only information about drug input was accessible. A specific compartmental structure for the pharmacokinetic–pharmacodynamic link was not assumed and the approach did not require that the concentration–effect relation to be known *a priori*. The objective of this report is to demonstrate and validate the proposed pharmacodynamic approach using the cardiac effect of alfentanil, as an example.

Alfentanil is a short-acting narcotic analgesic with a rapid onset of action (5) that produces a dose-dependent decrease in the heart rate in the intact animal (5–10) and isolated cardiac preparations (11,12). Previous results have found that in unanesthetized dogs the alfentanil plasma concentration–heart rate curves for increasing and decreasing concentrations did not overlap (6). The concentration–effect curves were displaced in parallel to higher concentration for decreasing concentrations, suggesting a disequilibrium between the plasma alfentanil concentration and the pharmacologic effect (heart rate). This presents a suitable test system for investigating the application of the proposed variable direction hysteresis pharmacodynamic approach.

MATERIALS AND METHODS

The results are derived from studies conducted using New Zealand White rabbits of either sex, varying in age and weighing 1.5 to 3.5 kg. The experimental protocol was approved by the institutional animal care and use review committee. Animals were housed individually in steel-lined cages in a light- and temperature-controlled environment and provided access to food and water *ad libitum* prior to the study. All studies were conducted in a light- and sound-attenuated chamber at approximately the same time of the day to minimize any extraneous effects unrelated to the drug. On the day of the study, food and water were removed at least 4 hr before the start of the experimental protocol. Animals were placed in a custom-designed restrainer and a 24-G, 19-mm intravenous catheter (Jelco, Critikon, Tampa, FL) was inserted in the marginal ear vein. ECG electrodes were inserted and the heart rate was monitored using a HP and Model 78901A mainframe interfaced to an analog-to-digital converter (Model DT2811, Data Translation, Inc., Marlboro, MA 01752). Using a sampling rate of 200 Hz, the number of R–R intervals in an epoch of approximately 20 sec was calculated and saved to a computer hard disk for subsequent analysis. After setting up the recording system, the animals remained undisturbed in the dark for at least 15 min before the experimental protocol was started.

The infusion scheme of alfentanil (Lot No. A08/1, Jannsen Research Foundation, 40 Kingsbridge Road, Piscataway, NJ 08855) employed in the experiments was designed to provide an opportunity to develop a versatile pharmacodynamic model and to test optimally the ability of the proposed approach to predict responses for future infusion schemes (Fig. 1). For the first 30 min no drug was infused but the heart rate was monitored to obtain a baseline signal. Three sets of 30-min infusions of alfentanil were administered, with 1 hr of recovery between the infusions. The third set of infusions differed from the first two so as to produce a suitable test case for the prediction of future infusion schemes. All drug infusions were done via a computer-controlled infusion pump (Pump 22, Harvard Apparatus, Inc., South Natick, MA 01760). A slow, constant infusion of normal saline was kept running for the entire 5-hr study period to keep the intravenous lines patent. The total volume of solution infused over the 5-hr study period was between 8 and 10 mL.

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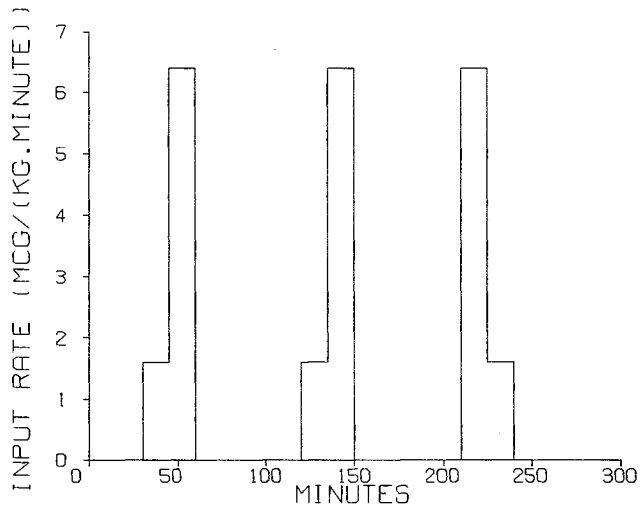

Fig. 1. Alfentanil infusion scheme employed to model the pharmacodynamic effect of the heart rate using the proposed hysteresis minimization approach.

Pharmacodynamic Modeling

The R–R intervals for each epoch were averaged to determine the average heart rate, which formed the basis for assessing the cardiovascular effect of alfentanil. Since plasma sampling is often not possible because the pharmacokinetic system may be changing too rapidly, it seems appropriate to formulate a pharmacodynamic model on the basis of the rate of drug infusion employed and the response(s) measured. Assuming that the dissociation between the plasma concentrations and the heart rate is due to a disequilibrium between the plasma drug concentration and the biophase, the pharmacodynamic effect of alfentanil, $E(t)$, may be modeled mathematically as

$$E(t) = N(c_b(t)) \tag{1}$$

$$c_b(t) = F\{r(t)\} \tag{2}$$

where $N(\ )$ is the *transduction function* that describes the concentration–effect relationship (13) and $c_b(t)$ represents the biophase drug concentration. The *pharmacokinetic predictor variable, r(t)*, which may represent plasma drug concentrations or rate of drug input, is related to the biophase drug concentration via a linear operator, $F\{\ \}$, which is termed the *biophase drug level predictor function.* The biophase drug level predictor function may, in general, be a response mapping operator (14) or, as in the present case, may take the form of a linear convolution-type operator:

$$c_b(t) = f(t) * \Phi(t) \tag{3}$$

where $f(t)$ represents the rate of drug input, $\Phi(t)$ is the *conduction function,* and the asterisk denotes a convolution. The conduction step encompasses all kinetic processes describing the transport of drug from the site of input to the biophase and may be approximated by a sum of exponentials,

$$\Phi(t) = \sum_{j=1}^{n} G_j e^{-\gamma_j t} \tag{4}$$

The biophase often does not have a physical form or structure but rather is a temporal abstraction that allows a mathematical model to be applied to describe the pharmacodynamics. The term "biophase" appears less presumptuous than the often used alternative, "effect site" (2,15), and is preferred.

Since the biophase drug level is usually distinct from the pharmacokinetic predictor variable, it is not possible to identify it uniquely. Rather, only the basic shape and form may be determined. To scale the biophase drug level appropriately, the conduction function was normalized to have an area of unity:

$$\int_0^\infty \Phi(t)dt = \sum_{j=1}^{n} \frac{G_j}{\gamma_j} = 1 \tag{5}$$

This normalization is preferred over other scalings because the AUCs of the biophase drug concentration and the pharmacokinetic predictor variable will then be equal.

$$\int_0^\infty c_b(t)dt = \int_0^\infty \Phi(t) * r(t)dt = \int_0^\infty \Phi(t)dt \int_0^\infty r(t)dt = \int_0^\infty r(t)dt \tag{6}$$

Furthermore, if the pharmacokinetic predictor variable is the plasma drug concentration, then the mean steady-state scaled biophase drug concentration will be equal to the mean steady-state plasma drug concentration. The normalized area scaling also seems desirable since, in the special case when a monoexponential conduction function is used, the results can be compared with the effect compartment pharmacodynamic approaches where k_{1e} is scaled to be equal to k_{e0}.

In order to obtain physiologically meaningful biophase drug levels, the conduction function is constrained to be nonnegative,

$$\Phi(t) \geq 0 \tag{7}$$

These constraints [Eqs. (5) and (7)] may be implemented by using an appropriate reparameterization scheme (16). Reparameterization schemes have been used previously in enforcing simple constraints in pharmacokinetic curve fitting using sums of exponentials (17); in constrained deconvolution (18), and in pharmacodynamics (3). A reparameterization scheme that allows maximum flexibility in the admissible shapes of the conduction function and satisfies the above constraints was implemented. For a biexponential conduction function

$$\Phi(t) = \sum_{j=1}^{2} G_j e^{-\gamma_j t}\ \gamma_j \geq 0 \tag{8}$$

the reparameterization scheme may be defined as

$$\gamma_1 = p_1 \tag{9}$$

$$\gamma_2 = \gamma_1 + p_2 = p_1 + p_2 \tag{10}$$

$$G_1 = p_3 \tag{11}$$

where $p_i > 0$.

To incorporate the equality constraint of Eq. (5), G_2 is defined in terms of the other parameters,

$$G_2 = (p_1 + p_2)\left[1 - \frac{p_3}{p_1}\right] \tag{12}$$

subject to $\Phi(0) \geq 0$. This scheme will ensure that the conduction function is nonnegative and will give rise to nonnegative biophase drug levels. This scheme is a complete reparameterization scheme in that it accommodates all possible biexponential shapes that satisfy the constraints (16). For $n \geq 2$ the following strategy may be employed:

$$\gamma_j = \sum_{k=1}^{j} p_k, \quad 1 \leq j \leq n \tag{13}$$

$$G_j = p_{n+j}, \quad 1 \leq j \leq n-1 \tag{14}$$

$$G_n = \gamma_n\left[1 - \sum_{j=1}^{n-1} \frac{G_j}{\gamma_j}\right] \tag{15}$$

where $p_j > 0$ for $j \leq 2n - 1$.

This is a partially complete reparameterization scheme. It is more flexible than a scheme that constrains all G_j values to be nonnegative, but it does not accommodate all possible functional forms.

A temporal plot of the effect (e.g., heart rate) against the pharmacokinetic predictor variable (plasma drug concentrations or drug input rates) often reveals a hysteresis. This precludes the identification of the intrinsic concentration–effect relationship because of a disequilibrium between the sampling site and the biophase. Pharmacodynamic models are used to determine a biophase drug concentration that is more closely related to the effect than the pharmacokinetic predictor variable. For a time-invariant and instantaneous transduction, the effect arising from a particular biophase drug concentration depends only on the concentration, and not on the time at which this concentration is attained. A particular biophase drug concentration gives rise to one and only one effect. However, the converse need not be true, i.e., a particular effect may arise from more than one concentration, accounting for the possibility of nonmonotonic transductions. For a correctly determined biophase drug concentration, the degree of hysteresis in a plot of the effect against the predicted biophase drug concentration will be the smallest possible.

In many cases the objective in pharmacodynamics is to identify the parameters of the conduction function (G_j's, γ_j's) that allows the prediction of a biophase drug concentration which yields a minimal hysteresis in the $c_b(t)$–$E(t)$ plot. The approach proposed here is a hysteresis minimization technique where the hysteresis size forms the objective function to be minimized. This transforms the problem of pharmacodynamics into one of a nonlinear optimization. An advantage of the use of hysteresis minimization approaches in pharmacodynamics is that a specific functional relationship is not necessary for the transduction function. This is in contrast to some compartmental approaches where a specific functional relationship, usually the sigmoid E_{max} model, frequently needs to be assumed. Such assumptions may sometimes be overly restrictive. The objective of determining an input-effect pharmacodynamic model is to identify a set of parameters that describe the conduction function (G_j, γ_j) so that the biophase drug concentration predicted by Eq. (3) yields a minimal hysteresis in the temporal c_b–E plot.

Several unidirectional methods have been proposed for quantifying the degree of hysteresis (2,3,19). However, these implicitly assume that the error in one of the regression variables can be neglected. Since both the effect and the predicted biophase drug concentration are subject to error, it appears more suitable to use a variable direction approach that accounts for error in both regression variables for calculating the hysteresis size (20). Recently, a variable-direction hysteresis minimization pharmacodynamic approach was proposed that incorporated this feature (4).

The validation of the variable-direction hysteresis minimization pharmacodynamic approach was done in two steps. In the first step, the conduction functions that gave the smallest possible hysteresis in a plot of the heart rate versus the predicted biophase concentration were determined using the first 180 min of data from a group of rabbits treated with alfentanil. This step is termed the model determination step. The nonlinear optimization was done using a modified derivative-free Nelder–Mead minimizer employed by the general purpose curve-fitting program, FUNFIT (21). To prevent scale-dependent bias in the optimization, the effect and predicted biophase level axes were normalized through the following linear transformation:

$$\hat{X} = \frac{X - X_{min}}{X_{max} - X_{min}} \tag{16}$$

This transforms the effect and biophase drug level axes to (0, 1) regardless of the relative magnitudes of the two variables.

In hysteresis minimization pharmacodynamic approaches the transduction relationship may be obtained independently of the conduction relation, and specific functional assumptions about the transdunction relationship are not necessary (3,4). However, for descriptive and predictive purposes a parametric representation may be desirable. Two alternative parametric representations of the transduction relationship (sigmoid E_{max} and cubic polynomial) were investigated for their ability to predict effects. The parametric functions were fit to the c_b–E pairs of the collapses hysteresis loop that had been sorted in ascending order of c_b:

$$E(t) = E_0 + \frac{E_{max} c_b(t)^n}{EC_{50}^n + c_b(t)^n} \tag{17}$$

$$E(t) = E_0 + \sum_{j=1}^{3} a_j c_b^j \tag{18}$$

Following the model determination step was a prediction step where the heart rate from 180 to 300 min was predicted using the conduction and transduction relationships determined from the data for the first 180 min. Since the data from 180 to 300 min were not used in the model determination step, this allowed the variable direction pharmacodynamic method to be assessed for its predictive ability. The predictive power was assessed by calculating a relative predictive quotient (RPQ), defined as

$$RPQ = 100 \sqrt{\frac{SS_{MD}/N_{MD}}{SS_P/N_P}} \quad (19)$$

where SS_{MD} and SS_P represent the sum of squared errors in the model determination and prediction steps, respectively, and N is the number of data points in the corresponding step. The RPQ allows a more realistic assessment of the predictive power of the proposed model compared to absolute measures because it assesses the prediction relative to the quality of the fitted (determined) model. Since a poorly determined model would normally result in poor predictions, the goodness of fit in the prediction step has to be assessed relative to the fit in the model determination step. The RPQ parameter provides one possible means of doing this. It is also important to ensure that the fitted model adequately describes the data in the model determination step. This can be assessed from the correlation coefficient of the model determination step.

RESULTS AND DISCUSSION

The results of a representative optimization (rabbit 0430) are shown in Fig. 2. The alfentanil infusion causes a decrease in the heart rate (dashed curve in Fig. 2A). Not unexpectedly, a plot of the heart rate against the drug input rate shows a distinct hysteresis (Fig. 2C) which obscures the transduction relationship. Upon completion of the proposed optimization, a biophase level predictor function is determined that allows the biophase drug concentration profile to be predicted (Fig. 2B). The solid curve in Fig. 2B represents the predicted biophase concentration obtained from Eq. (3). The dashed curve represents the heart rate. The predicted biophase drug concentration appears to be more closely related to the heart rate than the pharmacokinetic predictor variable (alfentanil infusion rate). A plot of the heart rate against the predicted biophase drug concentration is shown in Fig. 2D and indicates a collapsed loop that does not appear to have any significant hysteresis beyond that due to the normal variability in the data. From this figure it is relatively easy to discern the intrinsic biophase drug concentration–effect relationship.

The conduction function that optimally collapsed the hysteresis loop and was used to predict the biophase level for this particular optimization is shown in Fig. 3 as the nonmonotonic curve. The monotonically increasing curve represents the biophase equilibration profile. A biophase equilibration profile is determined from the conduction function and provides information regarding the dynamics at which the biophase equilibrates to a predicted steady-state drug concentration (22). Biophase equilibrium times that might be of particular interest are the t_{50} and the t_{95}, defined as the time it takes the biophase to equilibrate to 50 and 95% of the predicted biophase steady-state concentration, respectively, following a constant steady-state plasma concentration that is instantaneously achieved and maintained. These may be calculated by solving the following equation for t:

$$\frac{\int_0^{t_x} \Phi(u)du}{\int_0^{\infty} \Phi(u)du} = x/100 \qquad (x = 50,95) \quad (20)$$

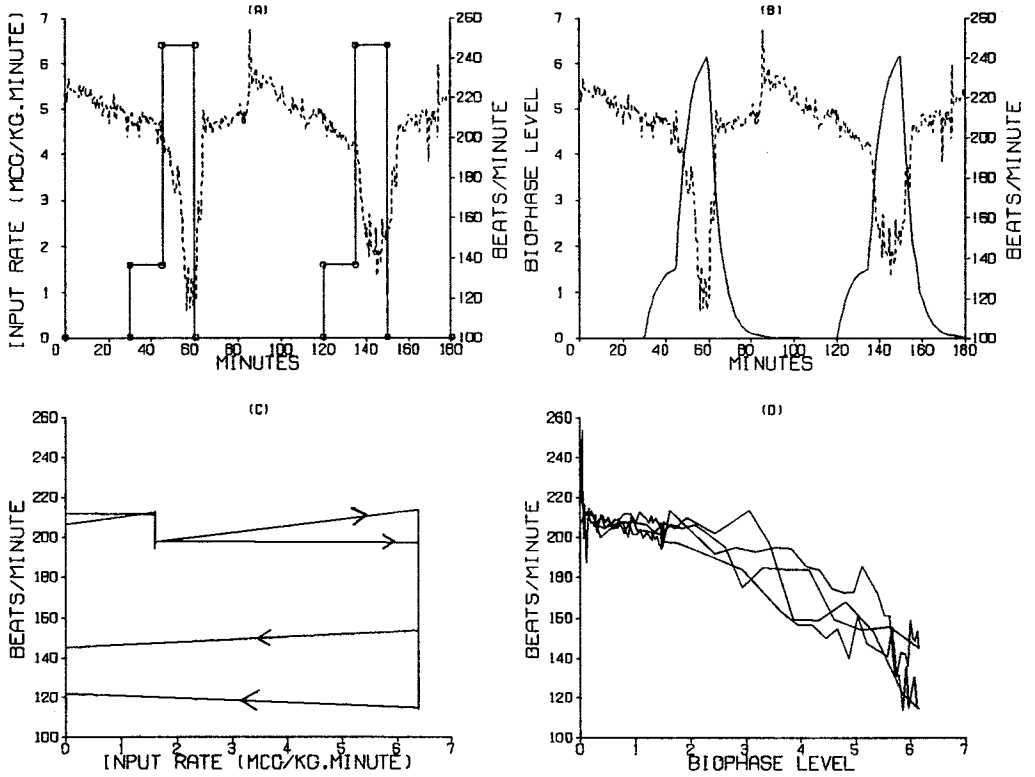

Fig. 2. Graphical illustration of the computational principles involved in the application of the proposed variable-direction hysteresis minimization approach. The example shown represents the effect of alfentanil on the heart rate of rabbit 0430 and uses the alfentanil input rate as the pharmacokinetic predictor variable.

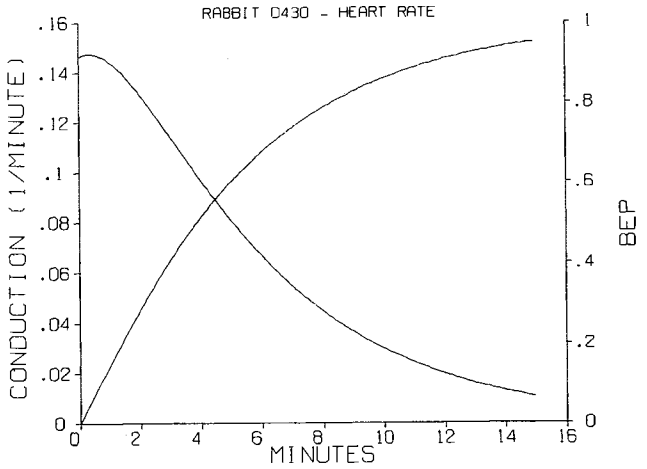

Fig. 3. Calculated conduction function used in predicting the biophase level and corresponding biophase equilibration profile (monotonically increasing curve) for rabbit 0430.

The t_{50} and t_{95} for this particular conduction were 3.9 and 14.9 min, respectively. The results of the other optimizations and corresponding equilibration times are summarized in Table I. The mean ± SD t_{50} and t_{95} for the conduction of alfentanil to the biophase were 7.4 ± 4.7 and 70.6 ± 33 min, respectively, excluding the results for rabbits 0221 and 0310. These two rabbits had a very slow conduction component that gave rise to apparently large biophase equilibration times.

The predictive power of the proposed hysteresis minimization approach for the animal used in the model determination step (rabbit 0430) is shown in Fig. 5. The top panel in Figure 5 shows the first 180 min of data that were used in determining the pharmacodynamic model. The solid curve represents the fitted model and was calculated from the optimized conduction and sigmoid E_{max} transduction relationships. The fitted model appears to describe the observed response adequately. In the bottom panel, the solid curve beyond 180 min represents the extrapolated (nonfitted) prediction using the conduction and parametric sigmoid E_{max} transduction relationships. The predicted curve describes the observed response reasonably well. There appears to be some variability in the heart rate response around 275 min that is less well described. The predictive power of the proposed approach was assessed using the RPQ. The RPQ for this particular prediction was 67.4%. This means that the predicted response is 67.4%, in agreement with the observed data in the prediction step. The RPQ provides a rational means of comparing the extrapolated prediction to the model determination step. It assesses the prediction relative to the model determined. The correlation coefficient of 0.93 for the model determination step indicates that the fitted model adequately describes the observed response in the model determination step. Together, these results indicate that the proposed model adequately describes the observed response and has a good predictive power.

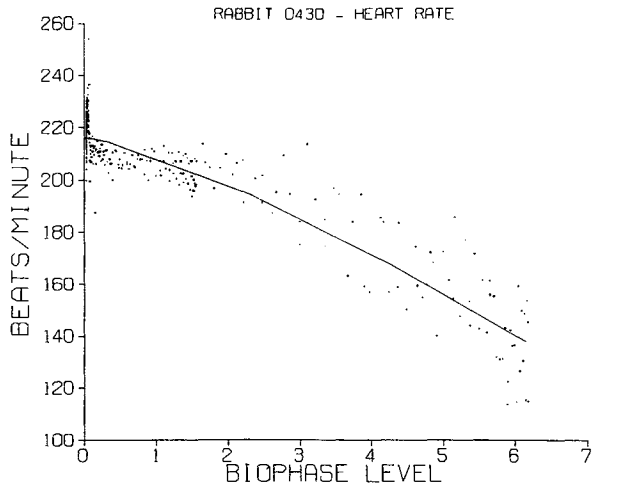

Fig. 4. Transduction relationship obtained by fitting a sigmoid E_{max} model to the points of the collapsed hysteresis loop sorted in order of increasing c_b.

The cubic polynomial and sigmoid E_{max} transduction functions and corresponding predictions for all the animals in the study are summarized in Tables II and III, respectively. Many of the transduction relationships were nearly linear, and for these the sigmoid E_{max} equation did not provide meaningful E_{max} and EC_{50} values. Such fits are indicated by asterisks in Table III. For the cubic polynomial transduction relationship, the mean (±SD) correlation coefficient of the model determination step was 0.87 ± 0.06 and the RPQ for the extrapolated predictions was 68.3 ± 27%. The correlation coefficient and RPQ for the sigmoid E_{max} transduction relationships were 0.88 ± 0.06 and 66.8 ± 28%, respectively. Both the cubic polynomial and the sigmoid E_{max} transduction relationships describe and predict the heart rate equally well, giving similar correlation coefficients and RPQs. The relatively high RPQs indicate that the proposed pharmacodynamic model has an acceptable predictive potential. Biological signals normally have a higher degree of variability than physical signals, and a correlation coefficient of greater than 0.85 indicates that the proposed pharmacodynamic model describes the observed response quite well.

The peak effects appear to be slightly better described than the effects corresponding to the times when the drug has been eliminated from the biophase for both forms of the transduction relationships considered. The above analysis assumes that the conduction and transduction relationships are stationary and that inductive drug effects (tolerance or sensitization) are relatively minor. There have been reports that alfentanil may exhibit acute tolerance (6), and it is conceivable that the poor prediction by the model to subsequent alfentanil administrations is actually a manifestation of this phenomenon. Models are at best a simplification of reality (23), a mathematical description believed to be important in describing and understanding the observed phenomena. They need be adequate only for the use to which they will be put. In the present case it appears that the proposed model adequately describes the observed response and has predictive power in extrapolating the response following future infusions. In the event that there are significant inductive drug effects, specific modifications of the generalized hysteresis minimization method can be implemented or the inductive effect can be modeled specifically (24–26).

Both the cubic polynomial and the sigmoid E_{max} transduction functions had similar descriptive and predictive

Table I. Alfentanil Pharmacodynamics in Rabbits: Parameters Describing the Alfentanil Conduction Function Determined Using the Proposed Hysteresis Minimization Approach and Corresponding Biophase Equilibration Times

Rabbit	G_1 ($\times 10^2$)	γ_1 ($min^{-1} \times 10^2$)	G_2	γ_2 ($min^{-1} \times 10^2$)	G_3	γ_3 ($min^{-1} \times 10^2$)	G_4	γ_4 ($min^{-1} \times 10^2$)	t_{50} (min)	t_{95} (min)
R1225	2.99	4.88	4.15×10^{-2}	10.2	-4.97×10^{-2}	26.6			10.6	52.2
R1228	1.44	2.83	60.3	149	56.0	149	−116	150	2.8	82.0
R0101	1.15	2.30	1.27	369	62.5	1310	−62.1	1340	1.0	100
R0104	0.961	1.90	3.82	145	4.43	153	−8.05	160	3.0	122
R0114	1.26	2.38	1.60×10^{-2}	5.58	7.89×10^{-2}	43.0			14.7	100
R0117	1.27	2.39	1.58×10^{-2}	5.51	8.12×10^{-2}	43.9			14.7	99.5
R0127	1.27	2.48	1.26×10^{-2}	4.83	3.58	108	−3.46	113	13.6	95.7
R0131	2.79	5.10	0.735	48.9	1.07	54.8	−1.76	58.6	5.4	47.0
R0203	1.53	2.91	0.563	45.2	0.415	48.3	−0.923	56.5	6.5	81.1
R0218	1.26	2.27	0.328	17.4	−0.315	21.8			14.2	106
R0221*	4.87	0.882	5.06×10^{-3}	1.71	1.40×10^{-2}	9.26			47.0	279
R0310*	0.257	0.507	5.05×10^{-3}	1.92	1.52	36.7	−1.49	37.8	48.5	457
R0324	1.41	2.67	0.641	42.2	1.93	48.8	−2.52	50.4	7.0	88.3
R0327	3.28	5.58	3.99×10^{-4}	6.21	0.153	37.7			5.2	44.3
R0330	7.35	11.9	1.09	58.1	3.74	61.7	−4.80	63.5	3.8	21.0
R0410	2.12	3.77	2.91×10^{-2}	8.71	9.37×10^{-2}	23.7	−0.101	34.5	11.7	64.7
R0427	15.3	20.9	0.160	22.9	−0.286	66.5			4.63	15.4
R0430	15.7	20.5	9.20×10^{-2}	22.6	−0.103	58.5			3.9	14.9
R0515	1.83	3.54	22.7	102	−22.7	105			3.8	66.1
Mean									11.7	102
SD									14	103
				Excluding animals (R0221 and R0310)						
Mean									7.4	70.6
SD									4.7	33.4

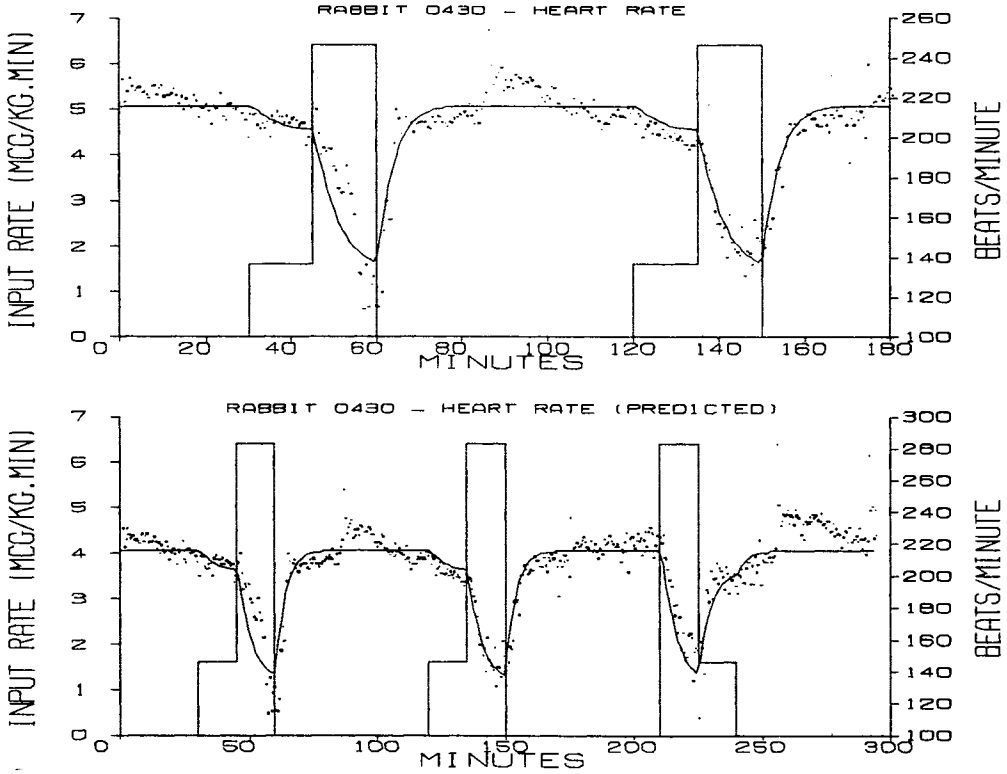

Fig. 5. Top: Model fitted to the first 180 min of data. Bottom: Predicted (extrapolated) heart rate (beyond 180 min) using the conduction function and sigmoid E_{max} transduction relationship obtained using data for the first 180 min (rabbit 0430).

Table II. Cubic Polynomial Transduction Function Parameters Describing the Effect of Alfentanil on the Heart Rate

Rabbit	E_0 (beats/min)	a_1	a_2	a_3	Correlation of fit	RPQ (%)[a]
1225	223	-2.28	-3.61	0.451	0.72	101
1228	224	-0.428	1.28	-1.28	0.95	53.5
0101	247	-4.40×10^{-3}	-12.0	1.63	0.91	109
0104	229	-0.392	1.17	-1.18	0.87	85.5
0114	217	-8.02×10^{-3}	-11.0	1.45	0.82	51.7
0117	208	-44.1	21.0	-3.90	0.83	104
0127	227	-6.91×10^{-3}	-19.8	3.55	0.88	36.9
0131	221	-6.71×10^{-6}	-3.82	0.459	0.81	34.6
0203	205	-8.28×10^{-6}	-4.65	0.565	0.92	35.7
0218	232	-52.9	17.2	-2.23	0.89	52.3
0221	200	-18.2	-10.6	4.20	0.86	33.1
0310	250	-4.04×10^{-6}	-29.1	7.75	0.85	68.7
0324	254	-47.1	-0.142	0.830	0.80	92.7
0327	234	-18.4	-2.98	0.647	0.87	73.6
0330	265	-24.9	-7.08×10^{-2}	6.17×10^{-3}	0.97	107
0410	219	-10.3	-1.43	0.437	0.80	35.0
0427	236	-18.8	3.67	-0.382	0.84	96.3
0430	217	-13.6	2.88	-0.479	0.94	68.3
0515	223	-3.25	-8.28	1.14	0.93	60.1
Mean					0.87	68.3
SD					0.06	27

[a] Measure of the goodness of fit of the prediction compared to the fitted model.

Table III. Sigmoid E_{max} Transduction Function Parameters Describing the Effect of Alfentanil on the Heart Rate

Rabbit	E_0 (beats/min)	E_{max}	EC_{50}	n	Correlation of fit	RPQ (%)[a]
1225	223	-123	6.56	1.63	0.72	101
1228	223	-181	4.50	5.21	0.95	52.5
0101	242	-85.8	2.28	6.29	0.93	106
0104	229	-93.1	3.69	6.36	0.87	84.5
0114*	218	-1020	19.3	1.48	0.82	51.0
0117	207	-215	4.65	1.89	0.86	99.2
0127	232	-230	4.46	1.45	0.89	34.8
0131*	223	-3420	298	1.08	0.84	33.1
0203*	208	-1670	93.1	1.15	0.93	38.0
0218	234	-229	11.6	0.64	0.89	48.1
0221	199	-55.1	1.12	2.14	0.86	33.2
0310	258	-63.3	0.87	2.47	0.90	53.9
0324*	257	-526	12.5	0.89	0.93	94.9
0327	233	-106	2.35	1.82	0.87	74.7
0330*	265	-511	13.6	1.16	0.97	108
0410	218	-34.9	1.41	2.60	0.81	34.2
0427	237	-579	108	0.75	0.85	93.9
0430*	216	-3270	95.4	1.35	0.93	67.4
0515	222	-124	3.46	2.00	0.93	60.5
Mean	229	-660	36.1	2.23	0.88	66.8
SD	17.6	1030	72.4	1.75	0.006	28
		Excluding animals marked with asterisks				
Mean	227	-128	3.91	2.88	0.88	66.8
SD	15.6	69.2	2.95	1.94	0.06	28

[a] Measure of the goodness of fit of the prediction compared to the fitted model.

power. The choice of which function to fit to the c_b–E pairs depends in part on the flexibility desired and on the particular use for the representation. It appears rational to make this choice on the basis of the shape of the collapsed loop upon completion of the optimization. Cubic splines provide the advantage of empirical fitting with a significant amount of flexibility. In some cases splines may not be desirable if significant extrapolations are anticipated in the c_b axis because splines can be unstable outside the range in which they were determined. The sigmoid E_{max} equation has the advantage of stability for extrapolation but does not accommodate all possible transductions.

CONCLUSIONS

The proposed variable direction hysteresis minimization pharmacodynamic approach presents a unique means of characterizing pharmacodynamics into two distinct steps, a conduction step which encompasses all kinetic processes giving rise to the transport of drug to the biophase and a transduction step that provides the intrinsic biophase drug concentration–effect relationship. The method assumes that the transduction is instantaneous and time-invariant. In the present context, the hysteresis is assumed to be due solely to a disequilibrium between the pharmacokinetic predictor variable and the biophase and not significantly due to inductive drug effects (tolerance or sensitization). The approach appears to be superior to some other hysteresis minimization techniques, as it also allows the input–effect pharmacodynamic relationships, where the pharmacokinetic predictor variable is the rate of drug input, to be investigated. It has the further advantage that specific structural assumptions about the pharmacodynamic model are not necessary.

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