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Simplified Warfarin Dose-response Pharmacodynamic Models

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Abstract

Warfarin is a frequently used oral anticoagulant for long-term prevention and treatment of thromboembolic events. Due to its narrow therapeutic range and large inter-individual dose-response variability, it is highly desirable to personalize warfarin dosing. However, the complexity of the conventional kinetic-pharmacodynamic (K-PD) models hampers the development of the personalized dose management. To avert this challenge, we propose simplified PD models for warfarin dose-response relationship, which is motivated by ideas from control theory. The simplified models were further applied to longitudinal data of 37 patients undergoing anticoagulation treatment using the standard two-stage approach and then compared with the conventional K-PD models. Data analysis shows that all models have a similar predictive ability, but the simplified models are most parsimonious.

Keywords

dose-response model; kinetic-pharmacodynamics; mixed-effects model; standard two-stage approach

1. Introduction

Warfarin is the most frequently used oral anticoagulant for prevention and treatment of thromboembolic events. The most common indications for its use include atrial fibrillation, post-myocardial infarction treatment, deep vein thrombosis, and installation of heart valves. Careful management of anticoagulation is required to minimize the risk of hemorrhagic events due to over-treatment but at the same time prevent the occurrence of ischemic necrosis or edemas in under-treated patients. Coagulation factors and anticoagulation proteins are produced mainly in the liver. They are biologically inactive unless carboxylated through a process that involves reduced vitamin K, regenerated from the vitamin K epoxide.

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Warfarin exerts its anticoagulation effect by interfering with the enzymatic reaction of vitamin K epoxide [1].

The key parameter describing the anticoagulation effect is the Prothrombin Time (PT), which is the time required for coagulation to occur *in vitro*. To standardize the inter-laboratory variability in PT, International Normalized Ratio (INR) has been introduced as the universally accepted anticoagulation metric. The INR is defined as the ratio of measured PT in a patient to a control PT measured in a World Health Organization (WHO) primary standard.

Warfarin dosing is one of the complicated dose managements due to its large inter-individual variability in the dose-response relationship. Patient-specific factors contribute to as much as 10-fold inter-individual variability in the maintenance dose of the drug [2]. To circumvent this challenge, pharmacokinetic-pharmacodynamic (PK-PD) models and kinetic-pharmacodynamic (K-PD) models have been proposed to analyze the dose-response relationship between warfarin and INR to improve understanding of warfarin pharmacology [3, 4, 5]. One drawback of such models that may prevent them from being used in day to day clinical practice is the large number of parameters; some of these parameters cannot be identified uniquely from sparse clinical data. To facilitate clinical use of predictive models for personalized warfarin dosing, it is therefore important to devise some parsimonious models with good predictive capabilities.

Therefore, we introduce so-called simplified pharmacodynamic (S-PD) models with minimal number of parameters required to sufficiently describe the time dynamics of the warfarin-INR dose-response relationship in this work. The proposed S-PD models were motivated by control theory [6, 7]. The control theory-based models have been employed for many areas of research, such as ventricular assist devices, hemodynamic variable control, cancer tumor growth and chemotherapy, insulin delivery to diabetic patients, and anemia management [7, 8]. The idea of the control theory is that the model is capable of representing the most essential properties of the process with a sufficient accuracy while using the minimum number of inputs and parameters. That is, the control theory-based models pursue a low- or reduced-order model to make it relatively easy and straightforward to calculate and implement, although the conventional models are in general more accurate than these models [7]. In other words, the control theory-based models aim to bring a trade-off of the model complexity and the predictive capacity [9].

The rest of this paper is organized as follows. Section 2 contains a detailed description of the conventional K-PD models and the proposed simplified models for warfarin dose-response relationship. In Section 3, the proposed models were applied to longitudinal data of 37 patients undergoing anticoagulation treatment and then compared with the conventional K-PD models. Finally, Section 4 provides some discussion and closed with conclusions.

2. Methods

Warfarin data

A longitudinal treatment data of patients from the anticoagulation clinic at the Veterans Affairs Medical Center in Louisville, KY were collected between years 2003–2010. Warfarin dose and the International Normalized Ratio (INR) for each patient were recorded. The frequency of INR measurement was every 3 days (initiation phase) to every 6 weeks (maintenance phase). All 175 patients were screened, 37 of them had sufficient data available for both initiation and maintenance phase and used their data for model estimation.

Kinetic-pharmacodynamic (K-PD) model

The full K-PD model (KPD7) was first constructed to relate the warfarin dose to INR with seven parameters, k_{de} , k_a , k_e , k_{in} , k_{out} , E_{max} , and ED_{50} . The warfarin K-PD was assumed to follow a transit compartment model with an indirect stimulation response model. Note that we chose one transit compartment based on our pre-analysis to find the optimal number of our warfarin data. The K-PD was then described by the system of the ordinary differential equations (ODEs) as follows:

$$\begin{aligned} \frac{dA(t)}{dt} &= -k_{de} \cdot A(t) \\ \frac{dT(t)}{dt} &= k_a A(t) - k_e T(t) \\ \frac{dR(t)}{dt} &= k_{in} \left(1 + E_{max} \frac{T(t)}{ED_{50} + T(t)} \right) - k_{out} R(t) \end{aligned} \quad (1)$$

$$(A(t), T(t), R(t))|_{t=0} = (Dose, 0, 0)$$

where $(A(t), T(t), R(t))$ were the amount in each of dose (drug), transit, and response compartments; k_{de} was the elimination rate constant; k_a and k_e are the absorption and the elimination rate constants of the transit compartment, respectively; k_{in} and k_{out} were the zero-order and the first-order constants, respectively; E_{max} was the maximum attainable stimulation of k_{in} ; and ED_{50} represented an infusion rate producing 50% of the effect. To simplify calculation, we used zero for the minimum value of INR instead of one in this study, resulting in $R(0) = 0$ in Equations (1)–(3).

In this study, we used five K-PD models, KPD7, KPD6, KPD5, KPD4, and KPD3, constructed by fixing one parameter at a time of the full K-PD model described above. That is, the KPD7 was the full K-PD model with seven parameters $\theta_7 = (k_{de}, k_a, k_e, k_{in}, k_{out}, E_{max}, ED_{50})$. The KPD6 is the K-PD with six parameters $\theta_6 = (k_a, k_e, k_{in}, k_{out}, E_{max}, ED_{50})$ by constraining $k_{de} = k_a$. The KPD5 has five parameters $\theta_5 = (k_e, k_{in}, k_{out}, E_{max}, ED_{50})$ after fixing $k_a = 2$ of KPD6. The KPD4 is the warfarin K-PD model with four parameters $\theta_4 = (k_{in}, k_{out}, E_{max}, ED_{50})$ after fixing $k_e = 0.02$ of KPD5. The KPD3 is the KPD4 with the constraint of $k_{out} = k_{in}$ having three parameters of $\theta_3 = (k_{in}, E_{max}, ED_{50})$. It should be noted that the full K-PD models were reduced to the smaller sub-models based on the general practice in this area.

Simplified warfarin kinetic-pharmacodynamic (S-PD) model

The motivation for the S-PD model comes from the control theory. Specifically, the S-PD model we proposed here was a low-order approximation of a higher-order (for more detail,

see Chapter 4 of Ref. 6). In this study, we considered two S-PD models, SPD2 (linear) and SPD3 (nonlinear). Both S-PD models were described by the systems of ordinary differential equations. These are the ODE models used in the SPD2:

$$\begin{aligned}\frac{dA(t)}{dt} &= -\frac{A(t)}{T_s} \\ \frac{dR(t)}{dt} &= k \cdot A(t) - \frac{R(t)}{T_s} \\ (A(t), R(t))|_{t=0} &= (Dose, 0)\end{aligned}\quad (2)$$

where $A(t)$, $R(t)$ were the amount in each of dose (drug) and response compartments; T_s was the time constant parameter; and k was the linear dose sensitivity parameter. The ODE model of SPD3 was as follows:

$$\begin{aligned}\frac{dA(t)}{dt} &= -\frac{A(t)}{T_s} \\ \frac{dR(t)}{dt} &= k_1 \cdot A(t) + k_2 \cdot R(t) - \frac{R(t)}{T_s} \\ \frac{dB(t)}{dt} &= -\frac{B(t)}{T_s} \\ (A(t), R(t), B(t))|_{t=0} &= (Dose, 0, Dose^2)\end{aligned}\quad (3)$$

where $A(t)$, $R(t)$, $B(t)$ were the amount in each of the first dose (drug), response, and the second dose (drug) compartments; T_s was the time constant parameter; and k_1 and k_2 were the dose sensitivity parameters. The time constant defined the amount of time it took for the response to achieve 63% of the final steady-state value after the model has been excited by a step dose increase. The dose sensitivity parameters k_1 (linear) and k_2 (quadratic) defined the increase (decrease) in steady-state response after a unit step (e.g. 1g) dose increase (decrease).

Unlike the nonlinear K-PD models, our S-PD models have closed-form solutions as follows, since they are linear ODEs:

$$\text{SPD2: } R(t) = k \cdot Dose(t) \cdot t \cdot \exp\left(-\frac{t}{T_s}\right), \quad (4)$$

$$\text{SPD3: } R(t) = (k_1 \cdot Dose(t) + k_2 \cdot Dose(t)^2) \cdot t \cdot \exp\left(-\frac{t}{T_s}\right); \quad (5)$$

where $Dose(t)$ was the administered dose of warfarin at time t . And the parameters of SPD3 and SPD2 are $\theta_{s2} = (k, T_s)$ and $\theta_{s3} = (k_1, k_2, T_s)$, respectively.

Parameter estimation

The mixed-effects model was considered to estimate the population-level parameters and the individual-level parameters in this work [10]. Several methods have been introduced for parameter estimation on the mixed-effects model, such as the Standard Two-Stage approach, the Global Two-Stage method, the Iterated Two-Stage Method, and so on (for details, see Ref. 11 and Ref. 12). Without loss of generality, we employed the Standard Two-Stage approach (STS) for parameter estimation. The STS consists of two stages. In the first stage, all the subject-specific parameters are estimated and then the population-level parameters are summarized using the subject-specific estimates at the second stage.

For each subject, the model parameters were estimated as follows. Suppose y_i is the log-transformed observed INR at time t_i , where $i = 1, \dots, N$ and N is the number of time points. Then the model has the form of

$$y_i|\theta, \sigma^2 \sim ND\{f(\theta, t_i), \sigma^2\}, i=1, \dots, N, \quad (6)$$

where ND stands for a normal distribution with variance σ^2 , $f(\theta, t_i) = \log(R(t_i))$ is the log-transformed response INR of warfarin, and θ is the parameter vectors corresponding to the model for the INR concentration $R(t_i)$. Then the -2 times log-likelihood function of (θ, σ^2) is

$$l(\theta, \sigma^2) = N \cdot \log(2\pi\sigma^2) + \frac{1}{2\sigma^2} \sum_{i=1}^N (y_i - f(\theta, t_i))^2. \quad (7)$$

The estimates of the parameters are obtained by minimizing the equation above:

$$(\hat{\theta}, \hat{\sigma}^2) = \operatorname{argmin}_{\theta, \sigma^2} l(\theta, \sigma^2). \quad (8)$$

In order to estimate the parameters, we used NONMEM [13] with first-order method, which is one of the most popular PK/PD analysis tools, based on the equations (7) and (8). When fitting the INR profiles, we used $(-30, -19.4, 5)$ for $\log(k_{in})$, $(-5, 1, 5)$ for $\log(E_{max})$, $(-20, 6.31, 10)$ for $\log(ED_{50})$, $(-20, -4.76, 5)$ for $\log(k_{out})$, $(-20, -3.9, 5)$ for $\log(k_e)$, $(-20, 0.7, 5)$ for $\log(k_{de})$, and $(-20, 0.7, 5)$ for $\log(k_a)$ as the initial values and the boundaries for K-PD models and $(0, 6, 5)$ for k , $(0, 0.214, 5)$ for k_1 , $(0, 0.0042, 5)$ for k_2 , and $(0, 50, 200)$ for T_s for S-PD models. After that, in order to obtain the population-level parameters, we calculated the empirical mean and the empirical variance-covariance matrix using the estimated subject-specific parameters.

3. Results

Figure 1 displays the scatter plots between the observed individual INR (x-axis) and the predicted individual INR (y-axis). The numbers in parenthesis indicate the square of the Pearson's correlation coefficient, which is the coefficient of determination (R^2). Note that the larger R^2 represents the better fitting. KPD7 has the largest R^2 and KPD3 has the smallest R^2 . The proposed model SPD2 has R^2 of 52.39%, but it increases to 58.89% for SPD3. Figure 2 shows the box plots of the individual INRs of each model. It seems that the predicted INRs of SPD2 and SPD3 are more closely resemble to the observed INRs in the sense that they have a wider range of INRs.

To evaluate the performance of each compartment model for fitting INRs, we further considered four criteria: mean squared error (MSE), $-2\log$ -likelihood ($-2\log L$), Akaike Information Criterion (AIC), and Bayesian Information Criterion (BIC). The best model is considered as the one with the lowest MSE, $-2\log L$, AIC and/or BIC. It is noteworthy that $-2\log L$ cannot be directly used for comparison between the K-PD and the S-PD models

since they are not nested models. The results of fitting INRs using the seven K-PD and S-PD models are reported in Table 1. In the table, KPD6 achieves the lowest MSE but is comparable with KPD7, while SPD2 and SPD3 achieve the best BIC and/or AIC. Overall, Table 1 and Figure 1 indicate that the proposed S-PD models are comparable to the conventional K-PD model. From now on, we selected the full model KPD7 as a gold standard and compared it with our proposed models, SPD2 and SPD3.

In Figure 3, the individual fitting curves of KPD7, SPD3, and SPD2 are displayed. All three models have similar predictive capabilities, with KPD7 providing slightly better fit in the maintenance phase in a few instances (e.g., Subjects 19 and 33). Most notably no model can reach the maximum INRs observed during the initiation phase in Subject 2, indicating that this measurement might be an outlier.

The boxplots of the estimates of the log-transformed parameters for KPD7, SPD3, and SPD2 are depicted in Figure 4, showing the inter-subject variability of each parameter. In addition, the empirical means and the empirical standard deviations (SDs) of each log-transformed estimate are printed in the top of the boxplots. We can see that the estimate of T_s for SPD2 has the lowest SD of 0.97 among the estimates, followed by the SDs of the estimates of T_s for SPD3 and k_{out} (1.22 and 1.36, respectively). Overall, the inter-subject variability of KPD7 is much larger than that of SPD2 and SPD3, suggesting that S-PD models should be less sensitive to the subject variability.

We can see the Pearson's correlation coefficients among the log-transformed estimates of the parameters of both K-PD and S-PD models in Table 2. As for KPD7 and SPD3, the parameters k_e , k_{in} , and k_{out} have significant relationships with k_2 and T_s , while k_1 has no significant relationship. As for KPD7 and SPD2, the parameter k in SPD2 is correlated with k_a , k_{in} , and k_{out} in KPD7 and the parameter T_s in SPD2 is significantly correlated with k_{in} and k_{out} in KPD7. As expected, the estimates of the parameters of SPD3 and SPD2 are significantly correlated to each other.

Furthermore, we also investigated the correlations between the average of INRs and the log-transformed parameters as shown in Table 3. The parameter k_e in KPD7 model is significantly correlated with the average INR, and, as for the S-PD models, the parameter T_s is significantly correlated to the average INR. Overall, it seems that the role of the parameter T_s of S-PD models is similar to that of the parameter k_e of KPD7.

4. Discussion and conclusions

One of the challenges in dose management is the complexity of dose-response models. To solve this problem, the simplified pharmacodynamic models are introduced in this study using the control theory.

The conventional K-PD models appear to have a larger inter-variability of the parameters than that of the proposed S-PD models as shown in Figure 4. In particular, we can see that the parameters, k_{de} , k_a , k_e , have a much larger coefficient of variance (CV) than others. This might explain why KPD7 has the smallest MSE than S-PD models. On the other hand, this larger inter-variability might be an indication of the effect of demographic variables. We,

therefore, investigated the correlations between the parameters and the demographic variables (age, height, weight) as depicted in Table 3. Most of the correlations are not significant except for k_e and T_s , suggesting that the large inter-variability is the characteristic of the parameter rather than the effect of the demographic variables.

The parameters of the proposed S-PD models are highly correlated to each other as can be seen in Table 2. This might be because each parameter in the simplified models corresponds to a combination of several parameters in the conventional models. On the other hand, all the absolute value of the correlation coefficients between (SPD2, SPD3) and KPD7 are less than 0.5, while those between SPD2 and SPD3 are larger than 0.5 except for that between k_1 and T_s in SPD3. Although SPD2 and SPD3 are developed as an alternative to KPD7, this implies that they can explain some of the variations that could not be explained by KPD7.

The proposed SPD2 and SPD3 have two advantages over KPD7. First, they have less number of parameters than KPD7 does, resulting in less complicated low-order models. The complicated models having a lot of unknown parameters often suffer from identifiability of the model parameters, while the simplified models could avoid this difficulty. Second, there exist the closed-form solutions for differential equations as Equations (4) and (5). This makes it possible for the simplified models to escape from the computationally intractable problems associated with the inverse problem of the complicated nonlinear ordinary differential equations. Nevertheless, it should be noted that the conventional K-PD model has the smallest MSE and its parameters are easy to interpret thanks to their concrete theoretical bases.

Overall, the statistical analysis with the limited data shows that both the conventional and the simplified PD models are comparable to each other in terms of the predictive ability. However, the proposed S-PD models are more parsimonious than the conventional K-PD models, resulting that they could be used in day to day clinical practice even with sparse clinical data.

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Figure 1. The scatter plots between the observed individual INRs and the predicted individual INRs

The numbers in parenthesis represent the coefficient of determination (R^2).

Figure 2.
The box plots of the individual INRs.

Figure 3.
The individual fitting curves of KPD7, SPD3, and SPD2.

Figure 4. The box plots of the log-transformed estimates of the parameters
 The numbers and the numbers in parentheses at the top of the plot represent the empirical mean and standard deviation of each log-transformed estimate, respectively.

Table 1

The results of the model comparison.

	AIC¹	BIC²	MSE³	-2LogL⁴
KPD7	-1.3243 * (2.3820) [#]	22.3237 (2.4288)	0.5930 (0.0669)	-17.3243 (2.3820)
KPD6	-4.1187 (2.5130)	16.5733 (2.5417)	0.5908 (0.0666)	-18.1187 (2.5130)
KPD5	-5.4540 (2.6349)	12.2820 (2.6260)	0.6194 (0.0698)	-17.4540 (2.6349)
KPD4	-7.0753 (2.4024)	7.7046 (2.3456)	0.6130 (0.0706)	-17.0753 (2.4024)
KPD3	-2.9287 (2.2424)	8.8953 (2.2248)	0.7347 (0.0724)	-10.9287 (2.2424)
SPD3	-7.1250 (2.1574)	4.6990 (2.1176)	0.6185 (0.0675)	-15.1250 (2.1574)
SPD2	-5.6342 (2.0887)	3.2338 (2.0497)	0.6669 (0.0642)	-11.6342 (2.0887)

¹ Akaike information criterion;

² Bayesian information criterion;

³ mean squared error;

⁴ -2 times log-transformed likelihood;

* Empirical mean;

[#] Empirical standard error.

Table 2
The correlation coefficients among the log-transformed estimates of parameters

The numbers in bold indicate significance at the 5% level.

	KPD7						SPD3			SPD2	
	k_a	k_e	k_{in}	k_{out}	E_{max}	E_{50}	k_1	k_2	T_s	k	T_s
k_{de}	-0.4176	0.0661	0.5566	-0.0417	-0.5194	-0.0460	-0.0394	-0.1740	0.0862	-0.3010	0.2074
k_a		-0.1613	-0.3762	0.0986	0.4914	0.5489	0.2048	0.1354	-0.2138	0.3353	-0.2775
k_e			0.2446	-0.0076	-0.2271	-0.0071	0.1141	-0.4007	0.3667	-0.0148	0.1368
KPD7				0.4681	-0.4724	0.0512	-0.1452	-0.4011	0.4351	-0.4081	0.3794
k_{out}					0.4035	-0.1884	-0.0286	-0.3922	0.4516	-0.3668	0.4169
E_{max}						-0.2844	0.1926	-0.0150	0.0208	0.1238	0.0321
E_{50}							0.0146	0.0602	-0.1109	0.1751	-0.2266
k_1								-0.1313	-0.4528	0.5557	-0.4527
SPD3									-0.7240	0.5155	-0.5172
k_2											
T_s										-0.7555	0.8365
SPD2											-0.9243
k											

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