Initialization of Warfarin Dosages Using Computer Modeling

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Objective: Software incorporating warfarin pharmacokinetics and pharmacodynamics, as well as a Bayesian regression method, was evaluated for accuracy in predicting steady-state dosages of warfarin during initialization of anticoagulation therapy. Design: A cohort study was used to compare computer predictions with physician-determined doses during a retrospective chart review of 42 patients. Patients: Forty-two patient charts were selected for monitoring anticoagulation initialization therapy. Of the 42 patients reviewed, 22 were excluded on the following bases: uncontrolled congestive heart failure; ongoing treatment with medications that interfered with warfarin metabolism or displaced warfarin from protein binding sites; recent treatment with fresh frozen plasma or vitamin K; or any bleeding disorders, sepsis, malabsorption or significant changes in liver and/or renal function. Main Outcome Measures: Using physician-determined International Normalized Ratios (INRs) as target levels for the software, the number of INR feedbacks needed to stabilize blood drug levels during initialization were compared between physicians and computer forecasting. Population parameters and sequentially measured INRs were used for evaluation. Results: Current oral anticoagulation protocols require significantly more measured INRs than computer forecasting to achieve steady-state dosages (9.5 v 4.4, respectively, \( p < 0.01 \)). Physicians showed a statistically significant pattern of underdosing patients (4.3 v 1.7 subtherapeutic INRs, respectively, \( p < 0.01 \)). Computer predictions tended to overdose patients but did not significantly increase the number of supratherapeutic INRs. This study showed that five INR inputs consistently gave accurate steady-state dosage predictions, and in many ways computer modeling was more effective than clinician-determined steady-state dosing in warfarin initialization. Conclusions: Computer modeling provides a reliable means of predicting initialization dosages for warfarin anticoagulation therapy with five INR inputs and therefore has merit in the clinical setting if used with sound clinical judgment.

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In an inpatient rehabilitation setting, physiatrists often assume primary care responsibilities for these patients undergoing active rehabilitation program, and adjustment of warfarin dosages for anticoagulation treatment is a common task. It is tedious and time-consuming and is often accomplished in a "trial-and-error" fashion, requiring numerous blood draws to reach a steady-state warfarin dosage. In the era of managed care, improving the efficiency of warfarin anticoagulation therapy is a must.

Warfarin is the oral anticoagulation drug that is most widely used today. Warfarin's pharmacokinetics and pharmacodynamics make its dosing complicated, requiring close scrutiny by clinicians for initialization and maintenance of dosages in each individual patient. Simplifying warfarin treatment would be a significant advance for anticoagulation therapy. Computer modeling of the pharmacokinetics and pharmacodynamics of warfarin provides a means to achieve this simplification.

Blood coagulation is a complex process, requiring platelets and various clotting factors. In the intrinsic and extrinsic pathways of blood coagulation, four essential clotting factors (II, VII, IX, X) are vitamin K dependent. Vitamin K is the cofactor required to convert the glutamate residues on factors II, VII, IX, and X to gamma-carboxyglutamate, so the factors can continue on in the blood clotting cascade. Warfarin (warfarin sodium, coumarin, Coumadin®) binds endogenous epoxide reductase that regenerates reduced vitamin K for clotting factor synthesis, and interferes with the blood clotting cascade. Thus, warfarin is clinically important for anticoagulation therapy in patients with pulmonary embolisms (PE), deep venous thrombosis (DVT), atrial fibrillation (A-fib), mechanical heart valve prostheses, and many other clinical conditions. However, warfarin’s complex pharmacokinetics and pharmacodynamics and its multiple interactions with other drugs make its initialization in anticoagulation therapy difficult. Periodic long-term follow-up also is necessary to ensure maintenance of a therapeutic anticoagulation status and avoid hemorrhagic complications. Changes in cardiovascular status, hepatobiliary function, renal function, nutritional status, and intake of alcohol and other medications can all potentially alter warfarin’s effectiveness, making dosing adjustments necessary.

At present, physicians determine dosage levels by drawing blood and measuring prothrombin times (PTs) to prescribe each individual dose until the patient’s blood drug levels have stabilized. An International Normalized Ratio (INR) is then calculated for the purpose of standardizing the thromboplastin reagent used in determining PTs:

\[
\text{INR} = \frac{\text{observed PT}}{\text{baseline PT}}
\]
where $\text{ISI} = \text{International Standardized Index (thromboplastin standardizing value as published by thromboplastin manufacturer)}.$

Initialization of warfarin is performed most commonly in the inpatient setting. For the same reasons, patients already established on a steady-state dosage in an outpatient clinical setting must return to the hospital to maintain accurate dosages within target PTs. Long-term anticoagulation therapy is thus difficult for the patient and costly. The objective of this project was to demonstrate the use of computer modeling for the initialization of warfarin treatment. Thus far, computer modeling has not yet been widely used in clinical warfarin management. The concept and value of computer modeling is not fully appreciated among clinicians. A significant portion of the patients were selected from the rehabilitation medicine inpatient population. Therefore, this method is potentially useful for physiatrists who usually assume primary responsibility for the initialization of warfarin treatment in inpatient rehabilitation settings.

**BACKGROUND**

Many attempts have been made to simplify individualized warfarin therapy. Sheiner and colleagues estimated population pharmacokinetic parameters to forecast individual parameters in a method known as Bayesian forecasting. This method is capable of predicting parameters for several drugs, including theophylline, phenytoin, lidocaine, and aminoglycosides. Other methods include trial-and-error dose titration and computer-generated estimates.

Computer software was developed recently to address warfarin’s pharmacokinetics and pharmacodynamics in relation to fixed parameters (ie, sex, age, height, weight) unique to each patient. This software uses a one-compartment open model for bolus administration of warfarin based on measured prothrombin response. Warfarin absorption is assumed to be relatively instantaneous and complete, and its pharmacokinetics is based on the following first-order elimination equations:

$$\frac{dC_p}{dt} = -kr * C_p$$

$$C_p(t) = C_p(0) * e^{-kt},$$

where

- $C_p =$ plasma warfarin concentration at any time, $t,$ during a dosing interval,
- $kr =$ first-order warfarin elimination rate constant.

The equations developed by Theophanous and Barille and modified by Svec and associates use population pharmacokinetic variables to predict a prothrombin response to warfarin therapy. The following equations describe warfarin’s pharmacodynamic response:

$$\frac{d\text{PCA}}{dt} = -m * \ln \frac{C_p}{C_{p_{\text{max}}}} - kd * \text{PCA}$$

$$\text{PCA}(t) = \text{PCA}(0) * e^{-kd(t)} - \left(\frac{mkr}{kd^2}(1 - e^{-kd(t)} - kd(t))\right),$$

where

- $\text{PCA} =$ prothrombin complex activity,
- $\text{PCA}(0) =$ initial prothrombin complex activity,
- $m =$ constant relating plasma warfarin concentration to clotting factor synthesis (slope of log dose-response curve),
- $kd =$ first-order rate constant for PCA degradation,
- $C_p =$ warfarin plasma concentration at the beginning of a specified dosing interval, and
- $C_{p_{\text{max}}} =$ warfarin plasma concentration at which clotting factor synthesis rate goes to zero.

These equations only apply when $C_p^{\text{min}} \leq C_p(0)e^{-kd(t)} \leq C_{p_{\text{max}}}$ ($C_p^{\text{min}} =$ minimum effective concentration). When plasma concentrations are $C_p > C_{p_{\text{max}}}$, prothrombin synthesis is completely blocked, and the following equation applies:

$$\text{PCA}(t) = \text{PCA}(0) * e^{-kd(t)},$$

where

- $\text{PCA}(0) =$ PCA at time $t$ when $C_p$ initially exceeds $C_{p_{\text{max}}}$, and
- $t =$ time required for $C_p$ to remain greater than $C_{p_{\text{max}}}.$

When plasma concentrations fall below the minimum effective concentration, $C_p^{\text{min}},$ there is no block of prothrombin synthesis, which can be demonstrated by the following equation:

$$\text{PCA}(t) = 100 - [(100 - \text{PCA}(0)) - e^{-kd(t)}],$$

where

- $100% =$ assumed control PCA value,
- $\text{PCA}(0) =$ PCA at time when $C_p < C_p^{\text{min}},$ and
- $t =$ time $C_p$ remains below $C_p^{\text{min}}.$

The computer also uses population pharmacodynamic variables, which are estimated by nonlinear regression using Bayesian forecasting. These values, derived from population parameters, use individual values that minimize sums of squared weighted residuals of parameter values (the observed PCA versus the predicted PCA). Using these parameters, the computer model can predict daily and steady-state dosages.

Bayesian forecasting accurately predicts dosages after four to five prothrombin ratio feedbacks. The software has been shown to be at least as effective as physician-directed dosing in inpatient and outpatient clinical settings and for prescribing accurate steady-state dosages.

**METHODS**

The records of 42 inpatients from a university medical center were reviewed retrospectively. All patients began warfarin therapy during their hospitalization. Indications for warfarin treatment included thromboembolic disorders such as DVT, PE, and A-fib, as well as mechanical heart prostheses. Daily dosages were given typically in the evening, and prothrombin times (PTs) were measured the following morning.
Table 1: Demographic and Clinical Characteristics

<table>
<thead>
<tr>
<th>Age</th>
<th>Range = 23–84</th>
<th>Mean = 59.9 ± 20.9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>11</td>
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</tr>
<tr>
<td>Male</td>
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<td></td>
</tr>
<tr>
<td>Weight</td>
<td>72.3 ± 15.6kg</td>
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</tr>
<tr>
<td>Height</td>
<td>65.4 ± 3.9in</td>
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<tr>
<td>Smokers</td>
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<tr>
<td>Primary diagnosis</td>
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<tr>
<td>Deep venous thrombosis</td>
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<td></td>
</tr>
<tr>
<td>Pulmonary embolus</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Atrial/mitral valve replacement</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Secondary diagnosis</td>
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<td></td>
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<tr>
<td>Congestive heart failure</td>
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<td></td>
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<tr>
<td>Stroke</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Controlled cancers</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Highest dose</td>
<td>12.5mg every day</td>
<td></td>
</tr>
<tr>
<td>Lower dose</td>
<td>1mg every day</td>
<td></td>
</tr>
</tbody>
</table>

NOTE. All patients were from a university medical center.

Exclusion criteria included the following: uncontrolled congestive heart failure; ongoing treatment with other medications that interfered with warfarin metabolism or displaced warfarin from protein binding sites; recent treatment with fresh frozen plasma or vitamin K; and any bleeding disorders, sepsis, malabsorption, or significant changes in liver and/or renal function. Concurrent treatment with intravenous heparin was allowed. As a result, only 20 patients were included in the study. (See table 1 for patient demographics and clinical characteristics.)

The number of PTs required to reach a steady-state therapeutic range was noted, along with dosages and patient characteristics. These values were entered into the computer. Predictions based on population parameters and sequential PT feedbacks (one to six) were then generated. Other factors of interest during chart review were concurrent medications and the reason(s) for anticoagulation therapy.

PTs were converted to INRs (see equation 1). Target INRs were determined by physicians and the number of subtherapeutic and supratherapeutic INRs required before reaching a therapeutic steady-state was noted, along with the number of blood draws necessary. Also noted was the number of INRs greater than 4.5, because this indicates potential bleeding complications. (See table 2 for all evaluation criteria.)

Relative predictive performance was determined using Student’s t test and root mean squared error (RMSE):

\[
\text{RMSE} = \sqrt{\text{mean prediction error}}
\]

\[
\text{prediction error} = (\text{predicted INR})^2 - (\text{true INR})^2.
\]

Mean prediction error and 95% confidence intervals were used to determine bias, and significance was defined as \( p < 0.05 \).

RESULTS

Twenty-two of the 42 patients were excluded, primarily because of ongoing treatment with drugs that interact with warfarin metabolism and protein binding, or to discharge from the hospital before reaching a therapeutic steady state. The remaining 20 patients were evaluated.

Five INR feedbacks proved to be clinically sufficient (RMSE = 0.66), with no clear difference in results from six feedbacks (RMSE = 0.68). Predictions based on population parameters only (RMSE = 1.33), one (RMSE = 1.45), and four (RMSE = 1.04) INR feedbacks were slightly worse; but predictions based on two (RMSE = 3.24) and three (RMSE = 2.59) INR feedbacks were significantly more inaccurate than those based on five. These results have also been shown by Svec3 (fig). Average prediction error consistently improved with each INR feedback from two to five.

Physicians ordered significantly more blood draws than necessary to find therapeutic dosages (9.45 ± 4.5 v 4.40 ± 2.0; \( p = 5E-05 \)). Physicians also tended to prescribe dosage levels conservatively, staying subtherapeutic for significantly more feedbacks (4.30 ± 1.8 v 1.65 ± 1.7; \( p = 1E-05 \)). The computer tended to overestimate its predictions, but this was not significant for the number of supratherapeutic INRs (1.95 ± 2.8 v 2.55 ± 2.2; \( p = 0.2257 \)) or the number of INRs greater than 4.5 (0.40 ± 1.2 v 0.75 ± 1.3; \( p = 0.1891 \)). (See table 2.)

DISCUSSION

The Theophanous and Barille model4 is valid only when serum warfarin concentrations correspond to the linear portion of the dose response curve (ie, >20% and <80% of the maximum).5 Some patients might have fallen out of this range, creating problems in the program’s predictions and skewing prediction error, as well as RMSE. The reliability of Bayesian forecasting depends on accurate initial population parameters, and a significant bias for predictions based on population parameters and initial feedbacks indicated a need to improve the accuracy of these parameters. These factors may explain the significantly large error observed when only one or two INRs were obtained for each individual. Clinically first two INR measurements may help to identify patients who are supersensitive to warfarin. The first and perhaps the second INR may not contribute much toward deriving a steady-state warfarin dosage. In addition, early INR measurements may be affected by cotreatment with intravenous heparin. Therefore, further reduction of blood

Table 2: Comparison of Physician Dosing Versus Computer Forecasting

<table>
<thead>
<tr>
<th>Physician</th>
<th>Computer</th>
<th>Significance of Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of feedbacks before reaching a steady-state therapeutic INR.</td>
<td>9.45 ± 4.5</td>
<td>4.40 ± 2.0</td>
</tr>
<tr>
<td>Number of subtherapeutic INRs before reaching a steady-state therapeutic INR.</td>
<td>4.30 ± 1.8</td>
<td>1.65 ± 1.7</td>
</tr>
<tr>
<td>Number of supratherapeutic INRs before reaching a steady-state therapeutic INR.</td>
<td>1.95 ± 2.8</td>
<td>2.55 ± 2.2</td>
</tr>
<tr>
<td>Number of INRs &gt;4.5 (significant for potential bleeding complications)</td>
<td>0.4 ± 1.2</td>
<td>0.75 ± 1.3</td>
</tr>
<tr>
<td>Highest INR</td>
<td>3.93 ± 1.8</td>
<td>4.37 ± 2.7</td>
</tr>
<tr>
<td>Lowest INR</td>
<td>1.1 ± 0.2</td>
<td>1.76 ± 0.6</td>
</tr>
<tr>
<td>Highest-lowest INR</td>
<td>2.82 ± 1.7</td>
<td>2.60 ± 2.4</td>
</tr>
</tbody>
</table>
draw during the first, and perhaps the second, day after the initialization of warfarin may be possible.

This study confirmed that up to five INR feedbacks can provide sufficient data for the computer to make accurate predictions of steady-state warfarin dosage. Further reduction of the number of blood draws down to three or four may be possible. Additionally, the computer predictions proved to be more effective than clinicians in finding therapeutic steady-state dosages during the initialization of warfarin therapy with respect to time and the number of blood draws. Future prospective studies evaluating various warfarin dosing schemes are warranted.

It is hoped that this study has shown that computer modeling may be used as a tool for clinicians to use in the initialization of warfarin anticoagulant treatment. This approach can certainly be incorporated into teaching medical students and training resident physician in warfarin anticoagulation management. Although computer modeling can aid and improve the clinical initialization of anticoagulation treatment, it cannot replace sound clinical judgment. The most efficient clinical drug management results from a combination of computer modeling and good clinical judgment.

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References

Supplier
a. Coumadin; Dupont Pharmaceuticals, Wilmington, DE 19880-0026.