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Use of Signals and Systems Engineering to Improve the Safety of Warfarin Initiation

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Abstract

Introduction—Warfarin-dosing algorithms combine clinical factors and dosing history with the current international normalized ratio (INR) to estimate the therapeutic warfarin dose.

Unfortunately, these approaches can result in an overdose if the INR is spuriously low. Our goal was to develop an alert mechanism based on prior INRs in addition to the current INR.

Patients and Methods—Using data from the Genetics Informatics Trial (GIFT), we analyzed warfarin dose estimates for days 3 through 11 that were 10% higher than an average of the previous two dose estimates. We fit a stepwise mixed model to current and prior dose estimates, and subsequently compared the root-mean-square-error (RMSE) in predicting the final therapeutic dose using the GIFT algorithm versus the mixed model.

Results—From 556 patients, 646 dosing records (75%) were randomly selected for the derivation cohort and 215 dosing records (25%) for the validation cohort. Using one prior dose estimate improved the accuracy of the warfarin dose estimate. Compared to a dose estimate based on current INR (GIFT algorithm), the mixed model reduced the RMSE in the derivation cohort by 0.0015 mg/day (RMSE 0.2079 vs. 0.2094; $p=0.039$). In the validation cohort, the RMSE reduction was not significant.

Conclusion—A mixed model of dose estimates based on the current and most recent INRs shows potential to improve the safety of warfarin dosing. Clinicians should be cautious about aggressively escalating the warfarin dose after an INR that is lower than expected.

Keywords

warfarin; patient safety; overdose; dosing algorithm; INR

Introduction

Spurious laboratory values and post-analytical errors can lead to erroneous dosing of drugs that have a narrow therapeutic index, such as warfarin. For example, a spuriously low International Normalized Ratio (INR) could potentially lead to a warfarin overdose and catastrophic hemorrhage. Computerized warfarin-dosing algorithms and nomograms [1–6] may actually increase this risk because they calculate the dose estimate based on clinical factors and the most current INR value [1–6].

In signals and systems engineering, a signal is a categorical variable that represents valuable information within a system. For example, a thermostat is a control system that receives input signal (i.e., an ambient temperature that is above or below preset thresholds) to make appropriate changes to the output signal (i.e., heating turns on or off). Input signals are passed through a filter and become modified output signals [7]. In this study, we evaluated the role of prior dose estimates in deriving a warning mechanism (“danger signal”) for an INR that is lower than expected. Applying the principles of data filtering, we re-calculated the dose estimate for days 3 through 11 of warfarin therapy when a day’s dose estimate was 10% higher than a weighted average of the previous two dose estimates. We hypothesized that compared to an algorithm based only on the current INR, an algorithm that also accounts for prior dose estimates would reduce prediction error. We illustrate the potential clinical benefit of our approach in a case study.

Methods

Records were obtained from patients enrolled in the Genetics InFormatics Trial (GIFT) to prevent DVT (ClinicalTrials.gov Identifier: NCT01006733). Patients in GIFT are at least 65 years old and receive one month of warfarin therapy after elective hip or knee arthroplasty. Patients are randomized to either clinical or pharmacogenetic dosing of warfarin and to a target INR of 1.8 or 2.5 [8]. All patients who had completed their participation in GIFT and had a dose estimate that was at least 10% greater than the weighted average of the previous two dose estimates were eligible for this study.

Dosing history for all GIFT patients was captured on www.WarfarinDosing.org. Warfarin dose estimates for days 3 through 11 were analyzed if the estimate was 10% higher than a weighted average of the previous two dose estimates. We focused on the first 11 days of therapy because patients are most susceptible to overdose during this time [9–10].

Patients were excluded if a therapeutic INR was not achieved after one month of warfarin therapy. Seventy-five percent of eligible patients were randomly selected for the derivation cohort while the remaining 25% was set aside for the validation cohort.

We quantified the root-mean-square-error (RMSE) in predicting the final dose estimate using the two approaches: (1) the day-specific dose estimate used in GIFT based on the current INR alone [11–14], and (2) a “weighted algorithm” that used a weighted average of the dose estimates based on the current INR and one (or more) prior INR value(s). The therapeutic warfarin dose was defined as in Appendix 2.

We calculated the weighted algorithm using a stepwise mixed model as shown by Equation 1. **A**, **B**, and **C** in Equation 1 are coefficients that were optimized using ordinary least-squares regression.

$$\ln(\text{weighted therapeutic dose}) = A \cdot \ln(\text{current}) + B \cdot \ln(\text{old}) + C \cdot \ln(\text{older}) \quad \text{Eq. 1}$$

Specifically, we offered into the mixed regression model: (1) **current**: the dose estimate based on the current INR; (2) **old**: the dose estimate based on most recent prior INR; and (3) **older**: the dose estimate based on the older INR. The therapy day and patient ID were treated as random variables. To avoid capturing idiosyncrasies in the derivation cohort, we used two constraints: (1) the average estimated warfarin dose in the entire cohort had to remain the same as with the “GIFT algorithm” and (2) no new intercept term could be added. The mixed model forward stepwise regression used a two-sided p-value < 0.05 to add a term (either **old** or **older**) and removed terms if the two-sided p-value > 0.10.

Results

Patient Characteristics

Records from 1300 GIFT patients were available for analysis. Seven hundred forty-four patients were excluded because they did not: (1) complete their warfarin therapy, (2) achieve a therapeutic INR, or (3) have one or more dose estimates 10% greater than the weighted average of the previous two dose estimates (Figure 1). Participants were elderly and mostly Caucasian (Table 1).

Mixed Model Analysis

We found (Equation 2) that a model based on the current INR and the most recent prior INR (**old** in Equation 1) was more accurate in predicting the final therapeutic dose than dosing based on the current INR alone. In Equation 2, **current** is the dose estimate based on the current INR and **prior** is the estimate of the dose estimate based on the most recent prior INR. Incorporating an **older** dose estimate, did not significantly improve accuracy and was not retained in the mixed model.

$$\ln(\text{weighted therapeutic dose}) = 0.849 \cdot \ln(\text{current}) + 0.171 \cdot \ln(\text{prior}) \quad \text{Eq. 2}$$

In the derivation cohort, Equation 2 reduced the RMSE by 0.0015 mg/day when compared to using the **current** INR alone (RMSE 0.2079 vs. 0.2094; $p=0.039$). In the validation cohort, the difference in RMSE was insignificant (-0.00045 ; $p=0.68$).

Discussion

Dosing Improvement

We demonstrated potential improved accuracy and safety of warfarin initiation by using signals and systems engineering. Compared to an algorithm based only on the current INR, Equation 2 was better at predicting the final dose: in the derivation cohort, it reduced the RSME by 0.0015 mg/d. As expected, the dose estimate based on the current INR was the key contributor to Equation 2 and its 0.849 coefficient dwarfed the 0.171 coefficient of the prior dose estimate. Disappointingly, in the validation cohort, Equation 2 did not improve accuracy compared to the GIFT dose estimate based on only the current INR. Therefore, the potential improvement in warfarin safety from this approach requires validation.

www.WarfarinDosing.org is a NIH-supported web application that uses an algorithm based on clinical information (and genotype, if available) to dose patients beginning warfarin therapy. www.WarfarinDosing.org is utilized in both arms of the Genetics InFormatics Trial (GIFT) of Warfarin to Prevent DVT. GIFT hypothesizes that pharmacogenetic dosing will improve the safety and efficacy of warfarin dosing. Presently, the website prompts no warning if an INR seems spuriously low.

The implementation of an alert mechanism to warn clinicians if an INR seems spurious could improve warfarin safety. Because warfarin causes more iatrogenic hospitalizations among the elderly than any other medication [9], even modest improvements in warfarin safety could improve population health. Given that a low INR is expected if the patient missed a dose or took less than prescribed, a warning based only on a low INR would have many false positives. Therefore, we used signals and systems engineering to develop an alert mechanism based on the current and older dose estimates, as these estimates incorporate knowledge of prior warfarin doses.

Implementation

In clinical practice, a clinician using WarfarinDosing.org would receive a pop-up alert if today's dose estimate is 10% higher than a weighted average of the previous two dose estimates. The alert would urge the clinician to recheck the INR soon and would recommend a dose based on Equation 2.

Implementing such an alert would improve the overall dosing algorithm by reducing the influence of spuriously low INR results on dose estimates and protecting patients from a potential warfarin overdose. Such an alert system would be particularly beneficial in busy clinical settings where some patients receive warfarin therapy without frequent INR monitoring. It could also provide a critical warning when point-of-care (POC) devices are used to measure the INR, since some studies show significant differences in INR values depending on the POC testing method used [12–13]. Regardless of the use of a computerized dosing algorithm, clinicians should be encouraged to consider a patient's

dosing history before prescribing a new dose that is more than 10% greater than recent dose estimates.

Potential Limitations and Future Work

Limitations of our study include a modest sample size that may have limited our ability to validate the mixed model (Equation 2). In addition, data for Equation 2 was derived from the GIFT trial, which enrolled only elderly participants. However, the prospective data collection and high monitoring standards of the trial provided accurate data. Finally, to take advantage of this and other computerized dosing algorithms, physicians must have access to an Internet-enabled computer.

Conclusion

Our study demonstrates that incorporating prior dose estimates into a warfarin-dosing algorithm can help to identify spuriously low INR values and potentially avoid warfarin overdoses. Currently, many algorithms are based only on the most recent INR value. As electronic medical record (EMR) software products begin to incorporate dosing algorithms, they should have an alert mechanism to avoid over- or under-dosing warfarin after possibly spurious INR values.

Abbreviations

INR	international normalized ratio
GIFT	Genetics Informatics Trial
DVT	deep vein thrombosis
RMSE	root mean square error
POC	point of care
EMR	electronic medical record

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Appendix 1: Case Study

A 67-year-old participant in GIFT was started on one month of warfarin (target INR 2.5) for thromboprophylaxis after knee arthroplasty. Table A.1 shows the INRs and doses estimated by www.WarfarinDosing.org. On post-operative day 5, the INR was only 1.1, which led to an increase her dose estimated by www.WarfarinDosing.org (to 5.5 mg/d) and subsequently to an INR of 4.4.

Table A.1

Post-operative INR and dosing history from www.WarfarinDosing.org for the GIFT patient described in the case study. On post-operative day 5, the patient was given a significantly higher dose due to the spuriously low INR of 1.1. Had the clinician been alerted by our algorithm to recheck the INR, the patient might not have overdosed on warfarin.

Appendix Table: INRs and daily dose estimates

Post-operative day	INR	Dose estimate (mg/d)
3	1.6	3.5
4	2.2	3.2
5	1.1	5.5

This patient would have benefitted from our alert mechanism. Because 5.5 mg/d is more than 10% higher than the weighted average of the previous two dose estimates of 3.2 and 3.5 mg, Equation 2 would have generated a lower dose estimate of: $\exp [0.849 \cdot \ln(5.5) + 0.171 \cdot \ln(3.2)] = 5.2$ mg/d and WarfarinDosing.org would have been configured to recommend re-checking the INR soon. In this case study, we demonstrated the potential improved safety of an alert algorithm that accounts for both the prior and current dose estimates.

Appendix 2: Definition of Therapeutic Dose and Dose Estimate

An INR was considered in the target range if it falls within 2–3 for patients with a target INR of 2.5 and within 1.4–2.2 for patients with a target INR of 1.8. A dose was considered therapeutic if it was taken for six or more days prior to and during a period of at least two consecutively measured INRs in the target range, three or more days apart. If the patient took an alternating dose, then the averaged dose over the past seven days was the therapeutic dose. If more than one dose met this definition, then the one nearest the end of the first month of therapy was deemed “therapeutic.” If only one INR was within target range during days 8–34, we estimated the therapeutic dose by averaging the seven doses prior to the INR.

The dose estimate was the therapeutic dose if the INR was at the target INR; otherwise, the dose estimate was the therapeutic INR adjusted for target INR using Eq. A.1. The coefficient in that equation (0.088 mg/INR units) was obtained from a prior pharmacogenetic algorithm whereby the coefficient was 0.08796 mg/INR [18].

$$\ln(dose\ estimate) = \ln(therapeutic\ dose) \cdot [1 - 0.088(therapeutic\ INR - Target\ INR)] \text{ Eq. A.1}$$

Figure 1.
Derivation of the study cohort

Table 1

Patient characteristics for derivation and validation cohorts.

	Derivation Cohort N=468 patients, 646 records	Validation Cohort N=193 patients, 215 records
Demographic Characteristics		
Age (mean, std)	71.9 (5.36)	71.0 (5.11)
Male (%)	169 (36.1)	67 (34.7)
Race (N, %)		
Caucasian	419 (89.5)	173 (89.6)
African American	39 (8.3)	15 (7.8)
Asian or Indian Subcontinent	6 (1.3)	2 (1.0)
Other	4 (0.9)	3 (1.6)
Ethnicity		
Hispanic (N, %)	14 (3.0)	5 (2.6)
BSA m2 (mean, std),	1.91 (0.3)	1.90 (0.3)
Clinical Characteristics (N, %)		
Smoking	22 (4.7)	4 (2.1)
Diabetes	77 (16.5)	25 (13.0)
Liver Disease	4 (0.9)	4 (2.1)
Baseline INR (mean, std)	1.01 (0.06)	1.01 (0.05)
Target INR (N, %)		
Target 1.8	286 (61.1)	126 (65.3)
Target 2.5	182 (38.9)	67 (34.7)
Primary Indication (N, %)		
Hip replacement	126 (26.9)	52 (26.9)
Knee replacement	342 (73.1)	141 (73.1)