Assessing Importance of Dietary Data in Anticoagulation Treatment

Peter Bronnum NIELSEN, Esben Haldrup ERIKSEN, Rasmus Thoft MILTHERS, Ole K. HEJLESEN

Department of Health Science and Technology, Aalborg University, Denmark

Abstract. This paper describes the outcome of including information on dietary intake in the attempt to predict International Normalized Ratio (INR) values. An already published model has been extended and is now tested with the additional dietary data and without it. When predicting INR values seven days into the future, the new proposed model outperforms the existing one. It is concluded that adding information on dietary intake improves the accuracy of INR predictions.

Keywords. disease management, oral anticoagulation treatment, INR, predictive model, decision support

1. Introduction

Oral anticoagulation agents such as warfarin are prescribed to an increasing number of patients enrolled for lifelong therapy with underlying disorders such as heart valve replacement, atria fibrillation and venous thromboembolism. Despite benefits, use of warfarin is known to be associated with adverse effects, e.g., haemorrhage if too much warfarin is given. Maintaining patients within a desired therapeutic range required for oral anticoagulation treatment (OAT) presents a challenge due to two factors: (1) a target International Normalized Ratio (INR) value bounded by a relatively narrow therapeutic range and (2) a variable biological effect of oral vitamin K antagonists [1].

Recommendations and guidelines for patients assigned to self-management of OAT have been published, and computerized decision support systems have been developed to aid self-management of OAT [2–4]. They handle the vitamin K dependent clotting factors and prothrombin time (PT) differently in order to quantify anticoagulant response and thus calculate the necessary maintenance doses of oral anticoagulant agents. Such systems might be able to help the patient decide how to regulate maintenance dose by utilizing knowledge of previously administered anticoagulant agents. Biological variability factors and sensitivity parameters are often included in these systems to adjust for within and between patient-variability to attain accurate maintenance dose predictions. Besides this variability, dietary intake is known to alter the INR levels [5].

This paper reports the outcome of incorporating information on patient’s dietary intake when predicting future INR values. The pharmacokinetic and pharmacodynamic
model and relationship between clotting factors and INR values are inspired by Vadher et al. [6].

2. Methods

2.1. Patient Data and Model Strategy

Five patients enrolled in self-management of OAT completed a data acquisition program. The collected data was utilized to retrospectively test the model’s ability to predict future INR levels in an uncontrolled environment, i.e., the patient’s everyday life. Approval from the Danish Data Protection Agency was obtained prior to the start of the data acquisition program. Medicinsk Ambulatorium Brædstrup Sygehus, Denmark, was responsible for patient recruitment and agreement through written informed consent and was obtained prior to data collection.

Model parameters were acquired for approximately four weeks and daily collected data consisted of the following: Warfarin intake, INR measurement, dietary intake, alcohol consumption, dietary supplements and according to the patients relevant incidents; time stamps to these parameters were included as well. A study population summary is given in Table 1.

| Table 1. Overview of data from five patients. Indications for OAT were heart valve replacement, deep venous thrombosis or atrial fibrillation. Abbreviation: TTR = Time in Therapeutic Range |
|---|---|---|---|
| No. of days | INR | TTR | Warfarin dose |
| Mean | 27.2 (sum 157) | 2.5 | 83.7 % | 2.5 mg |

2.2. Pharmacokinetic/Pharmacodynamic Model of Warfarin

In this study an already published model by Vadher et al. was extended by adding information of dietary intake [6].

For the sake of simplicity the model treats various proteins of the prothrombin complex as a single substance [7]. Concentration of prothrombin complex is determined by balance between synthesis and degeneration of clotting factors. By using a PT ratio to measure prothrombin complex activity it is possible to estimate synthesis rate of each clotting factor as a percentage of normal, where normal refers to clotting factor synthesis rates in a person with a PT ratio of one. This corresponds to no anticoagulant effect, in this case, no effect from warfarin. Warfarin absorption is assumed to be instantaneous due to relative long halftime, which neglects absorption rate [6, 7]. Halftime for warfarin is set to 36 hours and warfarin model, assuming a first order exponential decay, is a one compartment model as given in Eq. (1).

\[
W(t) = W(0) \cdot e^{-kt}
\]

where \( W(t) \) is concentration of warfarin in plasma at time-stamp \( t \), \( W(0) \) is initial post bolus warfarin and \( k \) is first-order elimination constant of warfarin. A commonly applied hyperbolic tangent function was utilized in the model to describe the action when warfarin is present in the plasma compartment. Model involved clotting factors are factor II, VII and X. Degeneration rate of clotting factors is assumed constant, but synthesis rate of these is affected by warfarin as described in Eq. (2).
\[
\frac{dF}{dt} = w \cdot F_{\text{syn}} - F_{\text{deg}} \quad \text{where} \quad w = 1 - \tanh(W(t) \cdot \text{warfsens}) \tag{2}
\]

\(F_{\text{syn}}\) and \(F_{\text{deg}}\) are synthesis and degeneration, respectively, of each clotting factor and \text{warfsens} is a time varying variable that describes the patient’s sensitivity to warfarin. When no clotting factor synthesis-inhibition due to warfarin, the relationship \(F_{\text{syn}}=F_{\text{deg}}=K_{F_c} \cdot 100\) is assumed true, where \(K_{F_c}\) is constant clearance rate of each particular clotting factor. The INR values are obtained from the fraction of involved clotting factors and calculated as in Eq. (3).

\[
\text{INR} = 1 + \sum_{i=1}^{3} a_i \left( \frac{100 - F_i}{100} \right)^{s_i} \tag{3}
\]

\(F_i\) are provided from Eq. (2) to each of the three clotting factors, \(s_i = [1.29, 3.95, 1.17]\) are clotting factor dependant variables, and \(a_i\) are time-varying variables that affect the contribution to changes in INR values from each \(F_i\).

2.3. Effect from Dietary Intake

Patients assigned to long-term OAT may be sensitive to fluctuating levels of dietary intake [8]. Stafford indicates the impact of adding information of dietary intake of vitamin K by stating, “part of the variability in a single patient’s response to warfarin over time probably arises from variation in the dietary intake of vitamin K” [9]. The synthesis of proteins induced by vitamin K absence can be explained by course of action of the vitamin K cycle. The conversion of Glu to Gla domains is dependent on vitamin K. Figure 1 provides an overview of involved actions of the vitamin K cycle concerning OAT. The elimination of vitamin K from plasma has been shown initially fast and then more slowly, plasma levels after 24 hours having fallen to 10–20% of peak level [10]. Thus, a first order compartment model seems sufficient assuming intake of vitamin K as a bolus and instantaneously absorption.

![Figure 1. Vitamin K is reduced either by a NADH dependent reductase activity reaction (1) or a reductase dependent on the conversion of di thiol into disulfide reaction (3) (shaded). Carboxylation reaction (2) is driven by a vitamin KH2 dependent carboxylase activity, which simultaneously converts vitamin KH2 into vitamin K epoxide. The last step in the vitamin K cycle reaction (3) is a reductase of vitamin K epoxide dependent on conversion of di thiol into disulfide. Reactions indicated by (3) are inhibited by anticoagulants as warfarin, thus dietary vitamin K sources are necessary to maintain hemostasis.](image)
Halftime of vitamin K in plasma has been reported to be 1.5–3 hours [7]. Clearance of vitamin K is significantly shorter relative to warfarin, thus it is chosen to compensate for this shortcoming of the model by prolonging the effect from Vitamin K by factor 15.

A dose-response relationship between different sources of vitamin K and their effect on INR has been published by Schurgers et al. [11]; this log sigmoid relationship will be utilized in the model as $VK_{\text{action}}$. The resulting calculation of INR values is given in Eq. (4).

$$INR = 1 + \sum_{i=1}^{3} a_i \left( \frac{100 - F_i}{100} \right)^{\delta_i} - VK_{\text{action}}$$

(4)

3. Results

Results from model INR prediction values are provided for predictions seven days into the future, as patients enrolled to self-management of OAT usually measure their INR value once a week. To depict how the model predicts within the seven-day time span, the contribution to Root Mean Square (RMS) errors for all patients evaluated each day is provided in Figure 2.

Figure 2. This figure shows the RMS error in INR values for each patient each day with (solid line) and without (dotted line) information of dietary intake. The thinner dotted line is the information contained in adding dietary vitamin K to the model as in Eq. (5) evaluated each of the seven days.

Assuming independence between vitamin K information and other unknown sources of contributions to prediction errors, the estimation of information contained in dietary vitamin K each day is calculated as in Eq. (5) and shown in Figure 2 as the thinner dotted line evaluated each of the seven days.

$$\text{Error}_{\text{noDiet}}^2 = \text{Error}_{\text{Diet}}^2 + VK_{\text{Info}}^2$$

$$VK_{\text{Info}} = \sqrt{\text{Error}_{\text{noDiet}}^2 - \text{Error}_{\text{Diet}}^2}$$

(5)
4. Discussion

Present paper has described the outcome of incorporating nutrition information into an already existing model utilized in INR value predictions.

Analysing Figure 2, it can be concluded that by adding information on nutrition data the model accuracy is increased by 0.1–0.2 INR values (thinner dotted line). From a system perspective, including an end-user, this could have an impact: The patient will be able to rely on predictions from the model and thus be able to change warfarin intake in the following period of time, thereby maintaining the INR values within the therapeutic range given correct information provided to the model. Though, further analysis including larger study population is needed to achieve statically significance of the reported results.

As the basic idea is to use the model in an adaptive process adjusting time-varying variables, it is desirable to provide high quality data to the model to achieve optimal adjustments of parameters and thus accurate predictions. To obtain high quality data a system could be designed in such a manner that the user, i.e., OAT patient, has minimum interference with the system. By reducing data registration burden, it is hypothesized that benefits of easier management of OAT will be favoured, and data registration subsequently will have higher concerns relative to benefits with more accurate predictions as consequence.

In conclusion, addition of nutrition data has proven to benefit predictions of INR values. Further assessment of this approach is encouraged in the light of need to assist OAT patients in self-management of their therapy.

References


