33rd Annual International Conference of the IEEE EMBS
Boston, Massachusetts USA, August 30 - September 3, 2011

Modeling the Effects of Bivalirudin in Cardiac Surgical Patients

Thomas Edrich*, Gyorgy Frendl, James D. Rawn, Yannis Paschalidis , *Member, IEEE

Abstract—**Bivalirudin is direct thrombin inhibitor used in patients with heparin-induced thrombocytopenia. A pharmacokinetic and –dynamic model that predicts the partial thromboplastin time (PTT) based on the past infusion rates of bivalirudin following dose adjustment would be useful to guide optimal therapy. In this retrospective study we randomized 132 patients to a derivation and a validation cohort, and tested two models. The first model is a single-state linear model; the other incorporates a non-linear element to account for renal elimination of bivalirudin. Both models predicted PTT changes equally well with root-mean squared errors of 15 to 16 seconds (Pearson correlation coefficients for both were 0.67). Intra- and inter-individual variability of response to bivalirudin was significant. Although a high percentage of patients had moderate to severe renal dysfunction at one point during the bivalirudin infusion, the non-linear model that incorporates variable renal clearance of drug did not perform better than the linear model. This finding persisted even in the subgroup analysis of patients with moderate and low estimated glomerular filtration rates.**

I. Introduction

Bivalirudin antagonizes the effect of thrombin in the blood-clotting cascade, thereby preventing complications from blood clotting. It is an alternative to heparin, especially in patients who may have a risk of heparin-induced thrombocytopenia (HIT). It is currently FDA-approved for short-term anticoagulation of patients undergoing cardiac catheterization to prevent complications due to undesired blood clots. However, it is also finding increasing use in surgical intensive care unit (ICU) patients who require anticoagulation for a period of days. As a rarely used drug, clinical experience with its dosing in this setting is sparse. Optimal dosing can be particularly challenging for inexperienced trainees. Yet, it is these physicians who are primarily responsible for adjusting the bivalirudin infusion rate to achieve a desired partial thromboplastin time (PTT) range. For full anticoagulation, the PTT should be increased from an average baseline of 30 seconds to a range of 60-80 seconds. Adequate anticoagulation is necessary to avoid the risk of clot formation, but overshooting increases the risk of bleeding. As there is considerable inter- and intra-individual variability in the response to bivalirudin, it is challenging to titrate the drug. A mathematical model to predict the PTT given the past history of bivalirudin infusion rates would be useful but has not been put forward.

In this investigation, a simple single-state linear model was developed and tested using retrospective data. A non-linear model which takes the renal elimination of bivalirudin into account was tested as well. In the future, a reliable model could be incorporated into a decision support tool to guide the clinician when dosing bivalirudin.

Manuscript submitted April 15, 2011. This work was supported in part by the STAR (Surgical ICU TrAnslational Research) Center at Brigham and Women's Hospital.

T. Edrich and G Frendl are with the Department of Anesthesia, Perioperative and Pain Medicine, Brigham and Women's Hospital, Boston, MA 02115, USA (phone: 617-732-8280; fax: 617-264-5230; e-mail: tedrich@partners.org).

J. D. Rawn is with the Division of Cardiac Surgery, Brigham and Women's Hospital, Boston, MA 02115, USA (e-mail: jrawn@partners.org).

Y. Paschalidis is with the Department of Electrical and Computer Engineering and Division of Systems Engineering, Boston University, Boston, MA 02215, USA (e-mail: yannisp@bu.edu).

II. Methods

A. Data Collection

In a retrospective chart review of 132 post-cardiac surgical ICU patients with actual or suspected HIT, the coagulation parameter PTT and the estimated glomerular filtration rate (eGFR), an indicator of renal function, was collected electronically. The eGFR is calculated using the MDRD equation [1]. The continuous infusion rate of bivalirudin was transcribed manually from the paper ICU flow sheets. Transfusions of clotting factors during the infusion of bivalirudin were recorded. Clinical complications that occurred during administration of bivalirudin were retrieved from the cardiac surgical database.

B. Models

Two pharmacokinetic and –dynamic models were designed using Matlab/Simulink® (Mathworks, Natick, MA) as shown in figure 1. The single-state linear model includes a gain, Tp, representing the elimination time constant. The constant k_PTT, provides for the translation from serum concentration to the site-effect (PTT). A second, non-linear model includes eGFR and was chosen to better reflect variable renal elimination in our patients. A table for translation from eGFR to elimination coefficient was included based on the package insert provided by the manufacturer of bivalirudin (The Medicines Company, Parsippany, NJ). Elimination via non-renally dependent plasma protease is modeled with the parameter T_protease. The fixed parameter k_dist reflects the volume of distribution of bivalirudin. Other, more complex models including parameters reflecting liver function and nutritional status (both affect coagulation) were considered but not implemented because insufficient data was available to fit the associated parameters.

C. Analysis

After randomly assigning 132 patients into equal derivation and validation cohorts, the linear and non-linear models were fitted to the derivation data. This was performed by minimizing the least squares of the error function resulting between the actual and predicted PTT. A trust-region reflective algorithm was applied and each reiteration of the algorithm included the simulation from all patients in the

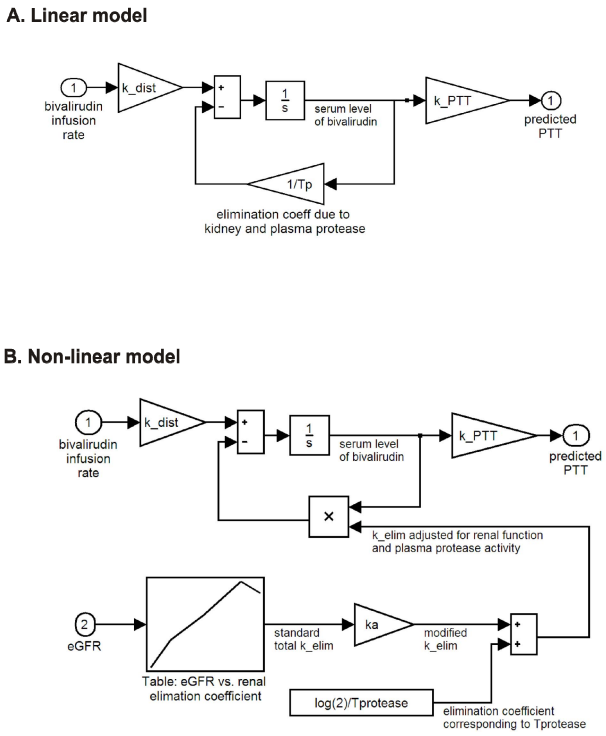

Fig. 1. Linear and non-linear models both produce a predicted PTT based on the known infusion rate of bivalirudin. In the linear model (Fig. 1A), the elimination coefficient, Tp, and the coefficient k_PTT are adjusted to fit the retrospective clinical data. In the non-linear model (Fig. 1B), the elimination coefficient is derived from a table and two adjustable parameters, ka and Tprotease, to reflect the effect of renal dysfunction. K_dist reflects volume of distribution and is fixed.

derivation group (n=66). Both models with the resulting parameters (Tp and k_PTT for the linear model, and ka, Tprotease, and k_PTT for the non-linear model) were then applied to each patient in the validation group. The resulting average root-mean square (RMS) errors and Pearson correlation coefficients were calculated.

D. Subgroup Analysis for Low eGFR

Using the same previously randomized derivation and validation cohorts, the models (linear and non-linear) were compared further by selecting only subgroups of patients with significant renal dysfunction. This was done for patients with an eGFR below 60 and again for those below 30 mL/min/1.73 m^2. As described above, derivation of a model for each subgroup occurred using the reduced derivation cohort, and validation was performed using the reduced validation cohort.

TABLE I
BASIC CHARACTERISTICS OF THE DERIVATION AND VALIDATION COHORTS

	Derivation cohort (n=66)	*Validation cohort (n=66)*
Mean PTT sampling intervals with standard deviation (hours)	9.7 ± 6.8 (mean ± STD)	10.4 ± 6.7 (mean ± STD)
Duration of bivalirudin infusion with standard deviation (days)	13.4 ± 11.1 (mean ± STD)	15.8 ± 13.0 (mean ± STD)

(PTT = partial thromboplastin time, STD = standard deviation)

TABLE II
OPTIMAL MODEL COEFFICIENTS AFTER FITTING TO THE DERIVATION COHORT, AND ERRORS WHEN TESTING IN THE VALIDATION COHORT

	Coefficients determined from derivation cohort	*RMS errors when tested in validation cohort (mean ± STD)*	*Pearson correlation coefficient when tested in validation cohort (mean ± STD)*
Linear model	Tp= 56 (min) kPPT= 1704 (sec*kg/mg)	15.6 ± 8.3 (sec)	0.67 ± 0.22
Non-linear model	ka= 0.41 Tprotease= 0.053 (min) k_PTT= 1996 (sec*kg/mg)	16.11 ± 6.61 (sec)	0.67 ± 0.23

(RMS = root-mean squared, STD = standard deviation)

TABLE III
CHANGE IN RMS ERRORS IN SECONDS FOR SUBGROUPS OF PATIENTS WITH EGFR <60 AND <30 ML/MIN/1.73 M^2

	RMS error when eGFR<60 mL/min/1.73 m^2 (=43 of 66 patients in derivation group and 52 of 66 patients in derivation group)	*RMS error when eGFR<30 mL/min/1.73 m^2 (=30 of 66 patients in validation group and 21 of 66 patients in validation group)*
Linear model	15.7	16.4
Non-linear model	15.9	17.0

(eGFR = estimated glomerular filtration rate)

E. Adverse Clinical Events

During administration of bivalirudin 12 patients had bleeding complications, most related to gastro-intestinal bleeding, and eleven patients were found to have a deep venous clot. Overall mortality was 29% but no instances were attributed to complications from bivalirudin anticoagulation.

III. RESULTS

All patients were cared for in the cardiac surgical ICU following valve repair or coronary bypass. The diagnosis of

HIT was made using clinical criteria such as unexpected platelet decrease by 50%, clinical stigmata of thombosis (HITT), and serologic testing for PF4 antibodies. As shown in table 1, the patients in both cohorts had bivalirudin infusions for a similar time period and the frequency of PTT sampling was similar. No patient had coagulation factor transfusions while receiving bivalirudin. Table 2 lists the coefficients for each model as determined from fitting to the derivation cohort. The mean RMS errors and Pearsons correlation coefficients were calculated by comparing the model performance to the actual PTT in the validation cohort. The time course of one representative patient in the validation cohort is shown in figure 2 with superimposed prediction from the linear model. When repeating the analysis for the subgroup of patients with renal dysfunction with eGFR of <60 and <30 mL/min/1.73 m^2, the derivation cohorts decreased to 43 and 30 patients, while the validation cohorts decreased to 52 and 21 patients, respectively. The RMS errors between the linear and non-linear models remained similar as shown in Table 3.

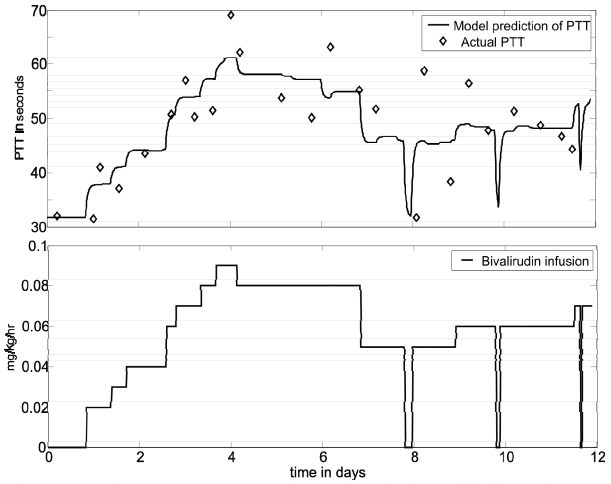

Fig. 2. Data from one representative patient in the validation cohort with superimposed prediction from the linear model. The bivalirudin infusion rate is plotted as well. The bivalirudin was stopped briefly several times for procedures.

IV. Discussion

In this retrospective study of post-cardiac surgery patients, two pharmacokinetic and –dynamic models were tested. After determining the best model coefficients for the randomized derivation cohort, we tested each model in the validation cohort and assessed its ability to predict the actual PTT continuously throughout the period of bivalirudin infusion. Both models yielded a reasonably accurate prediction of the actual PTT (RMS error 15-16 seconds and Pearson correlation coefficient 0.67 for both). Intra- and inter-individual variability was quite pronounced and accounts for this error. Although a general best-fit model is desirable for use in a patient population, a future model more suitable for the individual patient may incorporate an adaptive feature to adjust for this variability.

Significant findings were that the non-linear model, which incorporates effects of variable renal elimination, did not improve the predictive ability in comparison to the simple linear model. This was surprising as 66% percent in the derivation cohort and 78% in the validation cohort had at least one episode of moderate renal dysfunction (eGFR < 60 mL/min/1.73 m^2) during the course of treatment with bivalirudin. This finding persisted even in subgroup analysis that tested both models only on patients with moderate and severe renal dysfunction (eGFR < 60 and < 30 mL/min/1.73 m^2, respectively). This contrasts with a recent retrospective study on a mixed population which found evidence that the dose of bivalirudin required to fully anticoagulate declines predictably in the setting of renal dysfunction [2].
Several explanations may exist:

- In this study, the eGFR recovered after a transient dip in many patients and was in the normal range for the majority of the study period thus weakening the effect on the model fitting. Increasing the sample size may make the influence of renal clearance more prominent. Other studies that have found significant evidence of renal clearance have done so only in the setting of short-term anticoagulation for cardiac catheterization [3] or used only one pre-bivalirudin eGFR [2], not repeated measurements over time as in our study.
- Renal dysfunction may occur at a time when the patient is otherwise hypercoagulable which is commonly seen in the postoperative state. This may counteract the effect of the reduced renal elimination of bivalirudin. Our patients had all undergone cardiac surgery, most with cardiopulmonary bypass (CBP) which may alter the inflammatory response and coagulation and renal system. In comparison, the study by Kiser involved 38% cardiothoracic patients with an unspecified number receiving CBP [2].
- The component of renal elimination may be small in our patient population. A renal clearance of only 20% was found in a study of patients undergoing bivalirudin infusion up to 10 hours, finding that patients with renal dysfunction did not have a different response to bivalirudin [3].

The correlation of both models to the actual data was nearly identical. In the non-linear model, the optimal fit for the coefficient ka, which determines the strength of the influence of eGFR, was low at 0.41. Thus, the effect of variable eGFR was minimized, explaining why the correlation coefficients for both models were similar.

Clinical adverse events were recorded but contain many uncertainties such as onset time of clots and etiology of the gastro-intestinal bleeding. It is reassuring that no deaths were attributed to bleeding, however the morbidity due to underdosing bivalirudin is unknown.

The mathematical models described in this study may be found useful to test medication dosing strategies and may provide a mechanism for development and testing of nomograms such as those described by Kiser recently [4].

REFERENCES

[1] A. S. Levey, J. Coresh, T. Greene, L. A. Stevens, Y. L. Zhang, S. Hendriksen, J. W. Kusek, and F. Van Lente, "Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate," *Ann Intern Med,* vol. 145, pp. 247-54, Aug 15 2006.

[2] T. H. Kiser, J. C. Burch, P. M. Klem, and K. L. Hassell, "Safety, efficacy, and dosing requirements of bivalirudin in patients with heparin-induced thrombocytopenia," *Pharmacotherapy,* vol. 28, pp. 1115-24, Sep 2008.

[3] R. Robson, H. White, P. Aylward, and C. Frampton, "Bivalirudin pharmacokinetics and pharmacodynamics: effect of renal function, dose, and gender," *Clin Pharmacol Ther,* vol. 71, pp. 433-9, Jun 2002.

[4] T. H. Kiser, A. M. Mann, T. C. Trujillo, and K. L. Hassell, "Evaluation of empiric versus nomogram-based direct thrombin inhibitor management in patients with suspected heparin-induced thrombocytopenia," *Am J Hematol,* vol. 86, pp. 267-72, Mar.

[5] R. Robson, "The use of bivalirudin in patients with renal impairment," *J Invasive Cardiol,* vol. 12 Suppl F, pp. 33F-6, Dec 2000.