Using Biomarkers to Predict the Target Dose of Warfarin and Linezolid

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Objectives

1. **To use simulation and estimation techniques to evaluate the predictive performance and potential clinical utility of mechanistic models of biomarkers for dose individualization.**
2. **To illustrate the challenges of using biomarkers for dose individualization of warfarin and linezolid.**

Background

Warfarin is widely used as a treatment of venous thromboembolism and its capability to reduce the hazard of thromboembolic events has been unequivocally demonstrated. Variability between individuals, as well as a narrow therapeutic range are barriers to safe and effective warfarin therapy. Inadequate dose individualization contributes to under-utilization, 18-55% of patients who would benefit from warfarin do not receive it, and the amount of time spent within the therapeutic range is sub-optimal for many that do receive warfarin. An empirical model [1] for warfarin was unable to accurately predict doses above 7 mg/d [2]. A theory-based mechanistic model was developed to describe the pharmacokinetics using S- and R- warfarin and pharmacodynamics using the International Normalized Ratio (INR) (3).

Linezolid has strong antibacterial activity against aerobic Gram-positive cocci (GCP), methicillin-resistant coagulase-negative staphylococci, vancomycin-resistant enterococci and methicillin-resistant Staphylococcus aureus (MRSA). Thrombocytopenia and anemia are among the most important adverse effects of linezolid treatment. Linezolid-induced thrombocytopenia and anemia incidence varies considerably. Thrombocytopenia has been observed in about 10% of linezolid treated patients. Patients requiring treatment with linezolid frequently have impaired renal function and linezolid is extensively excreted by the kidneys. A pharmacokinetic and pharmacodynamic model for linezolid has been developed to predict the influence of renal function on linezolid concentration and concentration linked to the time course of development and recovery of thrombocytopenia [4].

Methods

Bayesian dose individualization methods, available at https://www.nextdose.org, have been developed for warfarin based on the INR as a biomarker and for linezolid based on total concentration (CT) and/or platelet count (PLT) as a biomarker.

A simulation-estimation procedure implemented in NONMEM 7.4.1 was used to individualize doses in 1000 simulated patients (Figure 1). For warfarin the initial dose was 6 mg on day 1 and 3 mg on days 2 and 3 and individual doses re-estimated after each INR measurement taken 12 h after the daily dose on days 3, 7, 10, 14, 21, 28, 35, 42, 49, and 56. An external data set of patient dose and INR was used to evaluate the warfarin model [2]. For linezolid the initial dose was 600 mg every 12 h on day 1 and individual doses re-estimated after either each CT or PLT measurement taken 6 h after the first daily dose on days 1 to 14. Predictive performance was quantified using bias (mean error, ME) and imprecision (root mean square error, RMSE).

Results

- Simulated predictions of the warfarin target dose were initially biased (ME: -0.56 mg/day; 95% CI: -0.59, -0.52 mg/day) and imprecise (RMSE: 2.1 mg/day). This diminished following INR measurements and dose adjustments. After six INR measurements and dose updates over 28 days, predictions were both unbiased (ME: -0.06 mg/day; 95% CI: -0.18, 0.07 mg/day) and more precise (RMSE: 0.66 mg/day. External evaluation of warfarin was unbiased (ME 0.14 mg/d; 95% CI: -0.91, 1.49 mg/day) with RMSE (0.67 mg/d) over the actual dose range of 0.75-11 mg/d.

- Simulated predictions of the linezolid target dose using CT were initially biased (ME: -34 mg/day; 95% CI: -41, -26 mg/day) and imprecise (RMSE: 245 mg/day). After 14 daily CT measurements and dose updates, predictions were both unbiased (ME: 2.1 mg/day; 95% CI: -14, 19 mg/day) and more precise (RMSE: 73 mg/day). In contrast, using PLT alone did not improve the ME or RMSE.

References

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Figure 1 Simulation-Estimation Process

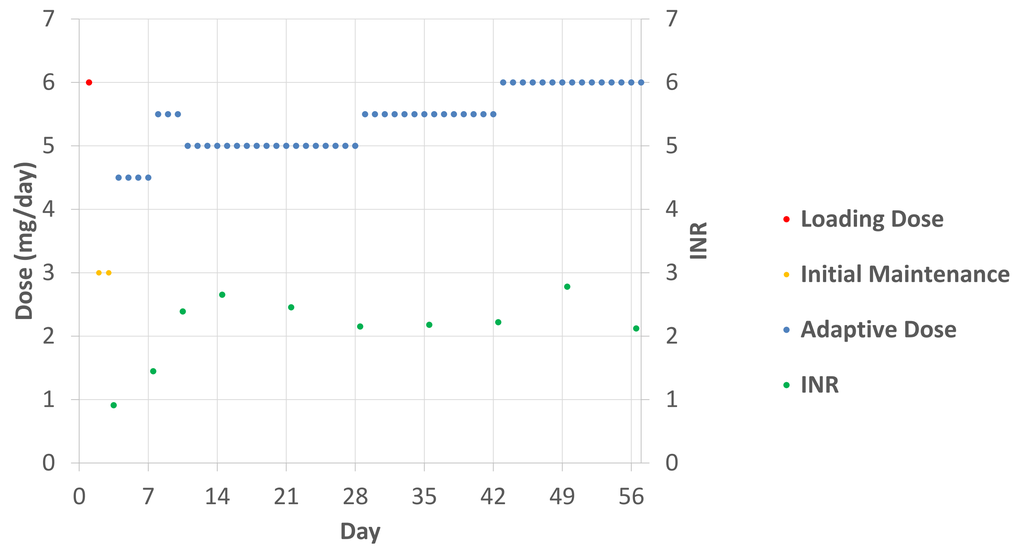


Figure 2 Warfarin Simulated Dose vs Predicted Dose

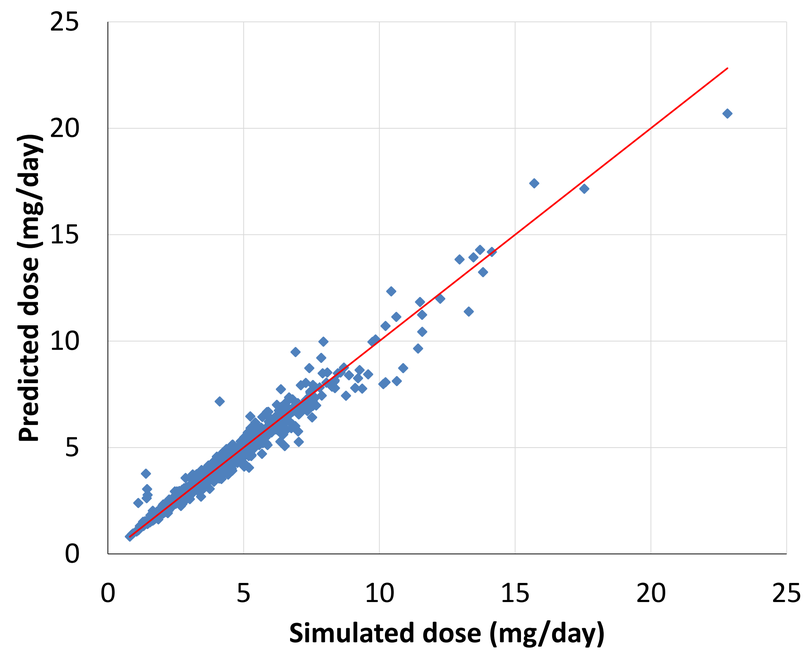
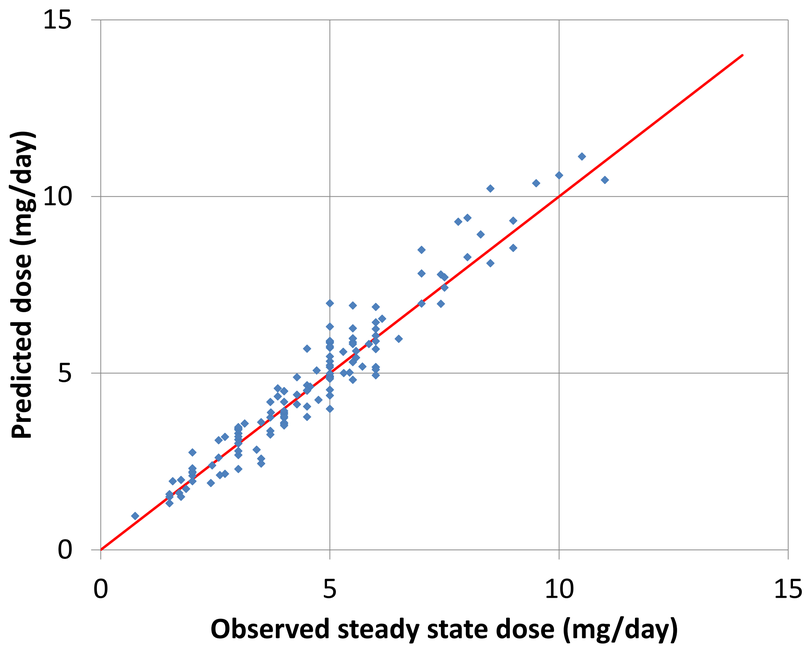


Figure 3 Warfarin Observed Dose vs Predicted Dose



Conclusions

- **Warfarin dose individualization using INR with a theory based PKPD model [3] is unbiased and precise as shown by simulation and external evaluation (Figure 2).**
- **Theory based warfarin dose individualization method is more accurate than an empirical method [1,2] using the same observations of steady state INR and doses (Figure 3).**
- **Linezolid dose individualization is not practical using platelet count alone. Dose individualization of linezolid should be based on measurement of linezolid concentration to improve antibacterial response and prevent the development of thrombocytopenia.**
- **Biomarker based dose individualization should be evaluated on a case by case basis. This analysis confirmed the value of using INR as a biomarker for warfarin dose but platelet count alone is not adequate for linezolid dosing.**

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