Development of a Bayesian forecasting method for warfarin dose individualisation

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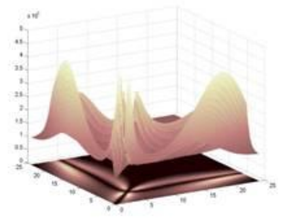

Background

- Warfarin is used to treat and prevent blood clots.
- Warfarin dosing is complicated by:
  - a large between subject variability in response.
  - a narrow therapeutic range.
  - a delay of 1-2 weeks to achieve a steady state response.
- Patient characteristics (e.g. weight, age) and genetic variability in CYP2C9 and VKORC1 explain 50-60% of warfarin dose variability [1]. Nearly one-half of the warfarin dose-response is currently unpredictable.
- Dose individualisation using Bayesian methods based on the INR response will account for all sources of dose variability.

Objectives

- To develop a Bayesian dose individualisation method for warfarin. There were five objectives:
  1. To identify PKPD models of warfarin from the literature.
  2. To evaluate these models.
  3. To develop an optimal design for Bayesian parameter control.
  4. To assess this design.
  5. To implement the model in TCIWorks.

Methods

1. A literature search identified 18 published PKPD models for warfarin.
2. Anticoagulant effect was simulated in MATLAB and compared to two external datasets [2,3] using visual predictive checks (VPCs).
3. INR sampling designs were evaluated. A MAP information matrix (FIM_{MAP}) was constructed in MATLAB given by:

$$FIM_{MAP} = J\Sigma^{-1}J' + \Omega^{-1}$$

The optimality criterion (ψ_{RSE}) was defined as the sum of squared relative standard error (SE) for the FIM_{MAP} given by:

$$\Psi_{RSE} = \sum_{i=1}^{p} \frac{SE_{MAP_i}}{\theta_{POP_i}} \qquad SE_{MAP} = \left(FIM_{MAP}\right)_{i,i}^{-0.5}; i = 1,\cdots,p$$

4. "True" parameter values were simulated from the full covariate model in MATLAB. Individual MAP estimators were determined and compared to "true" values as follows;

$$\text{Relative error} = \frac{\theta_{MAP_{jk}} - \theta_{TRUE_j}}{\theta_{TRUE_j}}$$

5. The warfarin model was entered into TCIWorks (www.tciworks.info). The INR response for a simulated patient with CYP2C9 *1/*1 and VKORC1 A/A genotypes was predicted. The prior parameter values were CL=0.348 L/hr and EC50=1.92 mg/L.

Results

1. Four models provided sufficient information to allow simulation [4,5,6,7]. A fifth was developed by our group from published data [8].

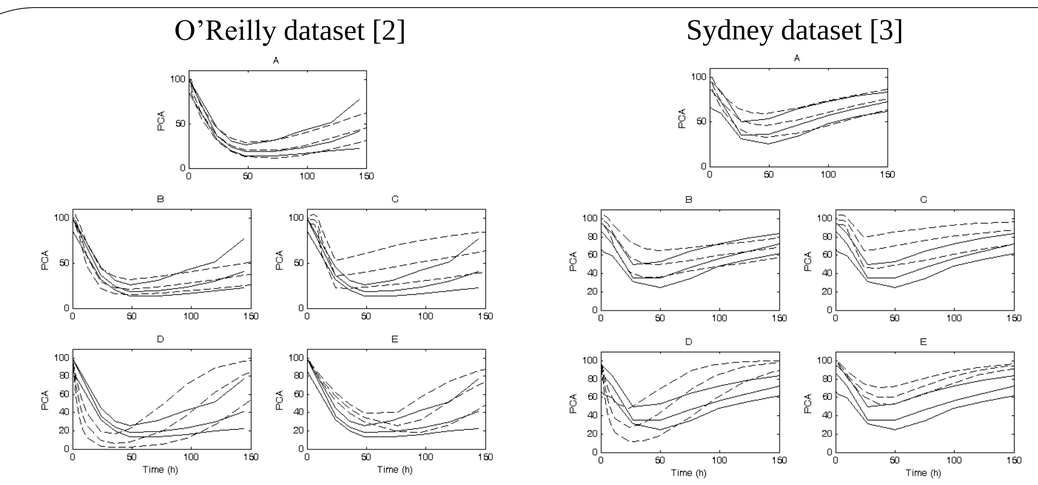

Figure 1. VPCs of PCA vs time for models (dashed) and external data (solid). Note: the Otago model (A) was developed from the O'Reilly dataset. Models: A [8], B [4] C [5], D [6] E [7].

2. A KPD from Hamberg et al [4] was selected.
3. The optimal sampling days were days 3,4,5,11,12,13 &14. Seven samples provided precise estimates of CL and EC50 (Table 1).

Table 1. Relative standard errors for clearance and EC50

		Relative standard error (%)		
Parameters	**Prior**	**5 samples**	**7 samples**	**9 samples**
CL (L/kg)	122	43	28	27
EC50 (mg/L)	83	37	25	25

4. Simulation-estimation indicated that as more samples became available the initial bias in CL and EC50 was reduced and the estimate of EC50 became more precise.

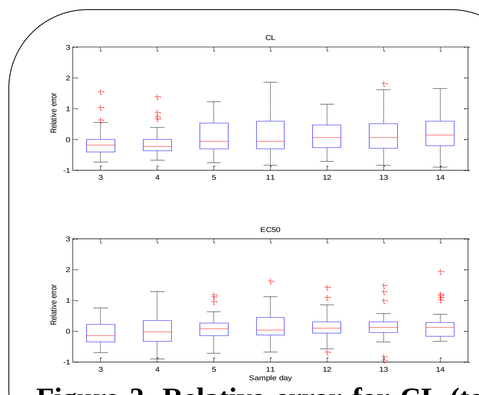

Figure 2. Relative error for CL (top) & EC50 (lower) for each sample day

5. TCIWorks predicted parameter values of 0.378 L/hr and 2.08 mg/L for CL and EC50 respectively. The tool accurately predicted a reduced EC50 value reflecting the A/A genotype.

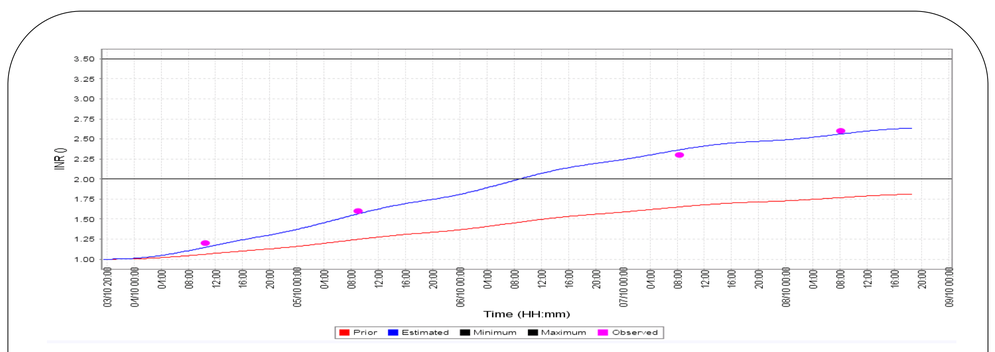

Figure 3. TCIWorks screen shot showing the "observed" INR values (dots), the prior predictions (red), and the individualised INR (blue)

Conclusions

- A Bayesian dose individualisation tool was developed.
- Research to assess the predictive performance of this tool is underway.

References

[1] Kurnik *et al*. Pharmacogenomics 2009;10:1955-1965. [2] O'Reilly *et al*. Circulation 1968;38:169-77. [3] Mohammed Abdul *et al* . Br J Pharmacol 2008;154:1691-700. [4] Hamberg *et al*. Clin Pharmacol Ther 2010;87:727-34. [5] Hamberg *et al*. Clin Pharmacol Ther 2007;81:529-38. [6] Pitsui *et al*. Ther Drug Monit 2003;25:36-40. [7] Yuen *et al*. J Pharmacokinet Pharmacodyn 2010;37:3-24. [8] Wright *et al* Pharm Res 2011;28:1100-11.