Evaluation of a Bayesian dose-individualisation method for enoxaparin

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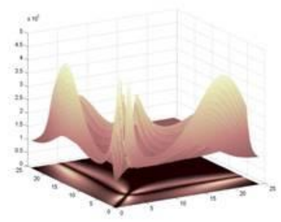

Background

- Enoxaparin is a widely used anticoagulant. Its treatment dose is based on total body weight (mg/kg) and its dosing frequency is adjusted dichotomously based on creatinine clearance (CLcr).
- Recent evidence has shown this dosing strategy to be suboptimal (resulting in bleeding or therapeutic failure).[1]
- Bayesian dose-individualisation has been proposed as a safe and effective alternative in order to achieve optimal anti-factor Xa concentrations (anti-Xa) during enoxaparin treatment.[2]
- TCIWorks is a dose-individualisation software that estimates the maximum a posteriori pharmacokinetic parameter values for an individual patient and provides predictions for future doses.

Objective

- To evaluate the predictive performance of a computerised Bayesian dose-individualisation method for enoxaparin (TCIWorks).

Methods

- A 2-compartment model with first order input and elimination was used as the prior model for enoxaparin.[3,4]
- Demographic data (**Table 1**), dosing history, and anti-Xa measurements of 109 patients who received enoxaparin treatment (Barras et al[5]) were entered into TCIWorks.
- There were a total of 238 anti-Xa measurements in the dataset: 109 first observations (mean = 4.1 mg/L), 98 second observations (mean = 8.6 mg/L), 26 third observations (mean = 6.9 mg/L), and 5 fourth observations (mean = 8 mg/L).
- The mean error (ME) and root mean squared error (RMSE) for the prior predictions (estimated from patient covariates) and posterior predictions (estimated from the posterior parameter estimates) to the future observed anti-Xa observations were calculated to determine the *bias* and *imprecision* of model predictions.
- The probability of a successful anti-Xa target (a peak of 5-10 mg/L and trough of 0-5 mg/L) was calculated.

Table 1. Patient demographics and other clinical characteristics.

Number of subjects	109
Male:Female	66:43
Weight (kg)	77 (43 – 120)
Height (cm)	170 (150 – 190)
Age (years)	61 (23 – 91)
CLcr (mL/min)	75 (26-174)

Results

Bias & Imprecision

- Bias and imprecision were significantly reduced after the inclusion of two observations; bias from -2.2 mg/L to -0.6 mg/L and imprecision from 3.3 mg/L to 1.7 mg/L (**Table 2**). These did not decrease further with inclusion of more observations. The prior model showed bias and imprecision which remained consistent for all observations ranging from -2.9 mg/L to -1.5 mg/L and 4.2 mg/L to 2.5 mg/L, respectively.
- The prior estimates of the 2nd and 3rd observations were less precise than the posterior estimates (variance ratio > 1).

Table 2. Mean error (95% CI) and root mean square error for the prior and posterior predictions. The variance ratios for observations two, three, and four are shown.

Observations	Prior		Posterior		Variance ratio
	ME	RMSE	ME	RMSE	
1	-1.5 (-1.9 to -1.1)	2.5	-	-	-
2	-2.9 (-3.5 to -2.3)	4.2	-2.2 (-2.7 to -1.7)	3.3	1.48*
3	-1.6 (-2.5 to -0.7)	2.8	-0.6 (-1.2 to -0.03)	1.7	2.24*
4	-2.3 (-3.9 to -0.7)	2.8	-0.6 (-2.3 to 1.1)	1.8	0.86

*** indicates statistical significance (P < 0.05)**

Probability of achieving target anti-Xa concentration

- The posterior predictions resulted in a higher probability of achieving target anti-Xa than the prior method (**Table 3**).

Table 3. Probability (in %) of achieving target anti-Xa concentration using the Prior and Posterior prediction methods.

Updated model	Probability of achieving target
Prior	69
Posterior with 1 observation	69
Posterior with 2 observations	90
Posterior with 3 observations	85

Conclusions

- TCIWorks provided accurate predictions of anti-Xa concentration.
- Using the MAP estimators to predict dose was superior to current enoxaparin dosing practice.
- There appears to be limited benefit in obtaining more than two anti-Xa observations during dose-individualisation.

References

1. Al-Sallami et al. NZMJ 2008; 121(1285):87-95 2. Al-Sallami et al. CPK 2010; 49(9):567-571 3 Green et al. BJCP 2003; 56 (1): 96-103
4. Green et al. BJCP 2005; 59 (3): 281-90 5. Barras et al. CPT 2008; 83(6):882-8