

PK/PD-Modeling (PK/PD) and Clinical Trial Simulation (CTS) of Early Clinical Data of a New Oral Direct Thrombin Inhibitor (Dabigatran Etxelate)

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Methods

Study 1: A multi-centre, open-label, dose escalation study in 314 patients and oral doses of 12.5, 25, 50, 100, 150, 200 and 300 mg bid or 150 and 300 mg od for a total of 6-10 days. On average, 16 blood samples were obtained from each patient and measured for dabigatran plasma concentrations using a validated LC-MS/MS method. In addition, aPTT and ECT were analysed in central laboratories.

Study 2: A multi-centre, parallel-group, double-blind study in 1973 patients with oral dosing of 50, 150 and 225 mg bid or 300 mg od or 40 mg enoxaparin for a total of 6-10 days. The primary efficacy outcome was the incidence of venous thromboembolism (detected by bilateral venography or symptomatic events) during treatment. In all patients about 3 samples (pre-dose)/patient were obtained, whereas in a subset of about 325 patients 13 plasma samples/patient were taken.

Data Analysis

Data from study 1 were used to derive the relationship between dose, dabigatran plasma concentrations and blood coagulation parameters (aPTT, ECT).

Data from study 2 were used to derive a relationship between dose, dabigatran exposure (AUC) and the incidence of VTE.

Simulations

The simulation platform consisted of a covariate distribution model; a PK model with covariates; PD models for ECT and aPTT; a PD model to link exposure to the incidence of thromboembolism; stochastic models for PK and PD parameter uncertainty, interindividual variability and residual error.

Population PK Model

The time course of dabigatran plasma concentrations was described by a 2-compartment first order elimination model with first order absorption and a lag-time. Covariates shown to influence the PK were CRCL, age, SCR and fasted serum gastrin (GAST).

Population PK/PD model for aPTT

A combined linear and nonlinear model described the relationship between concentrations and aPTT.

$$Y_{ij} = \left(\text{BASE} \cdot \exp(\eta_{1i}) + \frac{(\text{EMAX} \cdot \exp(\eta_{2i}) \cdot C_{pi})}{(\text{EC}_{50} \cdot \exp(\eta_{2i}) + C_{pi})} + (\text{SLOPE} \cdot \exp(\eta_{3i}) \cdot C_{pi}) \right) \cdot (1 + \epsilon_{ij})$$

E_{\max} and BASE were modeled as a function of time after surgery:

$$E_{\max} = \text{EMAX} \cdot \left(1 - \frac{\text{EMAX} \cdot \text{Time} / 24}{\text{ET} 50 + \text{Time} / 24} \right) \quad \text{BASE} = \text{BASO} \cdot \left(1 - \frac{\text{EMBA} \cdot \text{Time} / 24}{\text{ET} 50 + \text{Time} / 24} \right)$$

Population PK/PD model for ECT

A linear model described the relationship between concentrations and ECT.

$$Y_{ij} = (\text{BASE} \cdot \exp(\eta_{1i}) + \text{SLOPE} \cdot C_{pi}) \cdot (1 + \epsilon_{ij})$$

BASE and SLOPE were modeled as a function of time after surgery.

$$\text{BASE} = \text{BASO} \cdot \left(1 - \frac{\text{EMBA} \cdot \text{Time} / 24}{\text{ET} 50 + \text{Time} / 24} \right)$$

$$\text{SLOPE} = \text{SLOP} 0 \cdot (\exp(-K_m \cdot \text{Time} / 24)) + \text{SLOP} 1 \cdot (1 - \exp(-K_m \cdot \text{Time} / 24))$$

Covariate analysis did not reveal any significant covariate explaining interindividual variability in the PD parameters for both, aPTT and ECT measurements.

Population PK/PD model for incidence of venous thromboembolism

The probability of observing a deep vein thrombosis was modelled via logistic regression as a function of exposure (AUC) to dabigatran:

$$P = e^L / (1 + e^L); \quad L = (\text{BASE} + \text{SLOPE} \cdot \log(\text{AUC})) + \epsilon_i$$

The following covariates were identified to influence the relationship:

Type of surgery (hip or knee); alcohol consumption; smoking; age; substudy and type of anaesthesia (peripheral or general). All covariates acted on the slope parameter (Figure 4).

Results:

Question 1: How can the pharmacokinetics in patient be described and what are the relevant covariates influencing the pharmacokinetics of dabigatran?

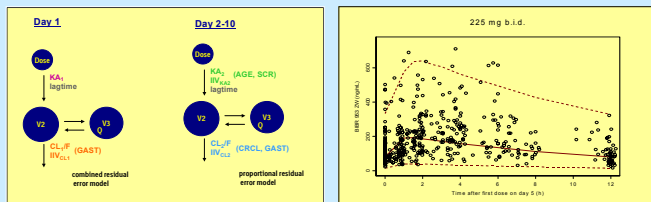


Figure 1: Schematic illustration of the PK model derived from study 1 (left) and a graph of the observed plasma concentration time profiles at steady-state for 225 mg bid in study 2 with the 95% prediction interval based on simulations using the PK model from study 1 (right).

- During the first 24 hours after surgery the pharmacokinetics of dabigatran are different compared to days >1.
- This is most likely due to alterations in gastric motility and gastric pH following surgery.
- As a consequence, the rate of absorption is reduced and interindividual variability in drug exposure is increased.
- Creatinine clearance was the most important covariate.

Question 2: How can the concentration-blood coagulation relationship be described and what are the relevant covariates influencing this relationship?

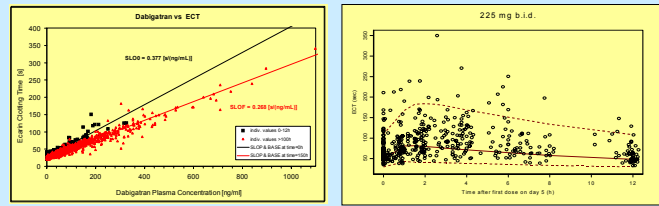


Figure 2: Schematic illustration of the ECT-plasma concentration relationship as derived from study 1 (left) and a graph of the observed ECT vs. time profiles at steady-state for 225 mg bid in study 2 with the 95% prediction interval based on simulations using the PD model from study 1 (right).

- No relevant covariates were identified.

Question 3: What would be an appropriate dosing regimen in renally impairment patients?

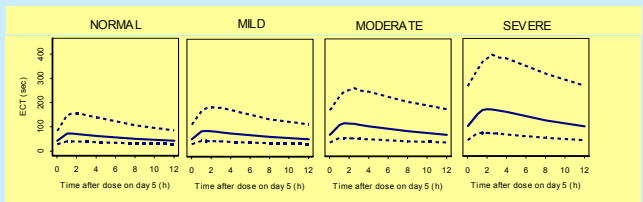


Figure 3: ECT versus time data from 100 replicate simulations were pooled together and the 50th (solid line) and 95th / 5th (dotted lines) point-wise percentiles were calculated for each renal group (Dose = 225 mg bid).

- Patients with severe renal impairment (10-30 ml/min) have an up to 4-fold increase in blood coagulation time prolongation whereas patients with moderate renal impairment (30-50 ml/min) have an approximate 2-fold increase in ECT.
- Because of the high interindividual variability the overlap in ECT-time profiles between the groups is large, no dose adjustment was recommended for study 2. The safety risk was judged as acceptable as patients stayed within the hospital for the duration of the study.

Question 4: What are the covariates effecting the relationship on the probability of observing a deep vein thrombosis and exposure and what would be the preferred dosing regimens for subsequent phase III/II trials?

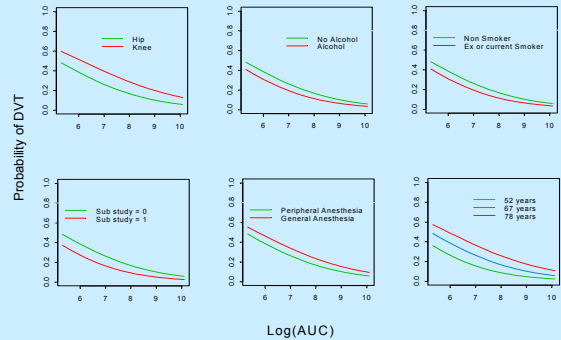


Figure 4: Influence of covariates on probability of DVT versus exposure (log AUC) relationship: Key covariates identified: type of surgery (hip/knee), alcohol consumption, smoking, sub-study (centre), type of anaesthesia (peripheral/general), age.

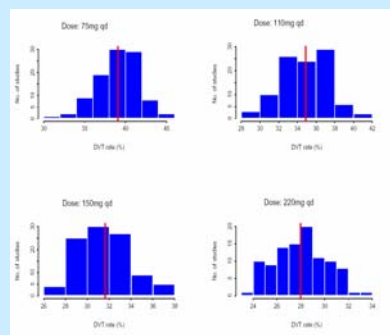


Figure 5: Clinical trial simulation of deep vein thrombosis (DVT) rates for different once daily dosing regimens based on the logistic regression model derived from study 2: 300 pts per dose group, 100 replicates. Distribution of study outcomes incl. mean of simulated rates.

- With QD doses of 110-220 mg dabigatran etexelate the phase III target DVT rates can be attained.

Conclusion:

- Consistent application of PK/PD-Modeling and Clinical Trial Simulation in early clinical drug development can help to answer important questions with respect to covariate effects, dose adjustments in special populations and dose finding.
- Additional studies to explore covariate effects can be avoided and, thus, development can be streamlined.