Pharmacometric Characterization of the Elimination of Dabigatran by Haemodialysis

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BACKGROUND

- Dabigatran etexilate is the orally administered prodrug of the direct thrombin inhibitor, dabigatran. Dabigatran has a half-life of 12–17 hours, is mainly cleared renally (~85%) and has low protein binding.
- It is approved for the prevention of stroke in patients with atrial fibrillation (AF) and for the primary prevention of thromboembolic events in patients undergoing hip or knee replacement surgery.
- In certain situations, such as the need for emergency surgery, rapid reversal of the anticoagulant effect may be required.
- Two phase I studies in patients with end-stage renal disease (ESRD) showed that haemodialysis is a useful method for removing dabigatran from the blood and reversing the anticoagulant effect.[1,2] However, there is currently no clinical recommendation for optimized elimination of dabigatran by haemodialysis (e.g., flow rates, filter type or duration of dialysis).

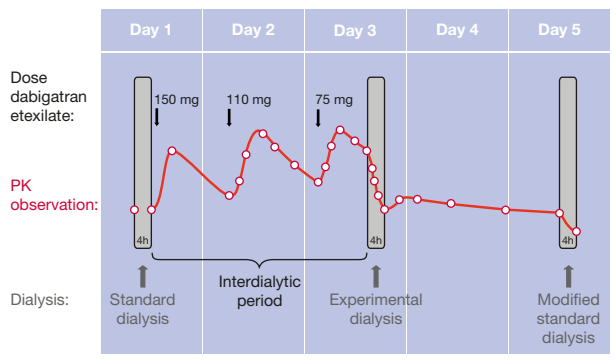
OBJECTIVES

- To characterize the effect of haemodialysis at different blood flow rates on the pharmacokinetics (PK) of dabigatran using pharmacometric approaches.
- To evaluate, by simulation, the effects of different clinically relevant haemodialysis settings in order to assess their potential impact on the elimination of dabigatran in non-ESRD situations.

METHODS

- In a randomized, open-label, fixed-sequence, phase I study,[1] ESRD patients received three doses of dabigatran in each of two study periods (Figure 1).

Figure 1: Study design for a single period



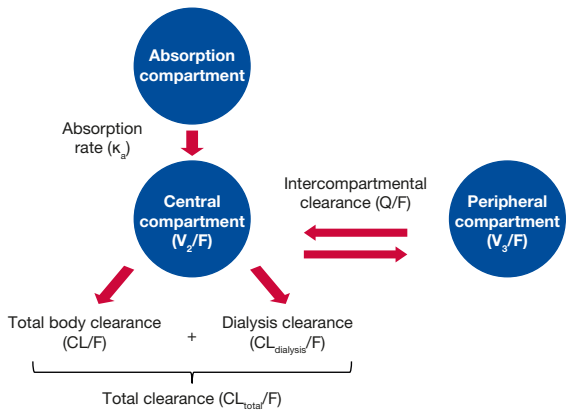
- Haemodialysis was performed with a dialysis flow rate of 700 mL/min. Target blood flow rates were 200 mL/min in the first period and 400 mL/min in the second period. Free and glucuronidated dabigatran were measured by high-performance liquid chromatography tandem mass spectrometry.[1]
- Data analysis, performed using NONMEM® and SAS, was based on a population PK model originally developed to optimize the design of the phase I study.[3] The model was refined to fit the data and then used for various simulations:
  - Scenario 1 simulated variations in the haemodialysis filter properties, such as: manufacturer, membrane surface area (20% reduction), low- vs. high-flux membrane, membrane material and a 'worst case' combining several effects; these were mimicked by varying the dialysis clearance by –5, –10, –20, +10% and –40%, respectively. Different blood flow and dialysis flow rates were also simulated. Other settings were as in the phase I study.
  - Scenario 2 explored the maximum redistribution effect.
  - Scenario 3 tested variations in renal function and duration of dialysis.
- Scenarios 2 and 3 simulated patients with AF receiving dabigatran 150 mg twice daily and used PK parameter estimates from the RE-LY® trial.[4]
- The model was retrospectively evaluated by predicting the plasma concentration time course of a patient undergoing dialysis from a literature report.[5] Model parameters were set for a typical patient in RE-LY® and matching the initial dabigatran concentration and dialysis conditions in the case report.

RESULTS

Population PK Model

- Data from all seven ESRD patients, including 28 dialysis sessions and 308 plasma samples, were available.
- A two-compartment model with first-order absorption and a lag time best described the PK of dabigatran in this setting (Figure 2). The apparent dabigatran total body clearance in subjects with ESRD was estimated at 12.4 L/h. An apparent dialysis clearance was implemented in parallel to describe the accelerated drug clearance caused by haemodialysis (> 0 during haemodialysis; 0 during the interdialytic periods).

Figure 2: Schematic illustration of the final PK model



- The effect of blood flow rate was best described using the Michaels equation.[6] By doubling the blood flow from 200 to 400 mL/min, the dialysis clearance increased by 30%, resulting in additional reduction of the dabigatran plasma concentration by only about 8%.
- The final model estimated all parameters with good precision (relative standard errors between 4.6 and 48.5%) (Table 1).

Table 1: Parameter estimates from the final population PK model

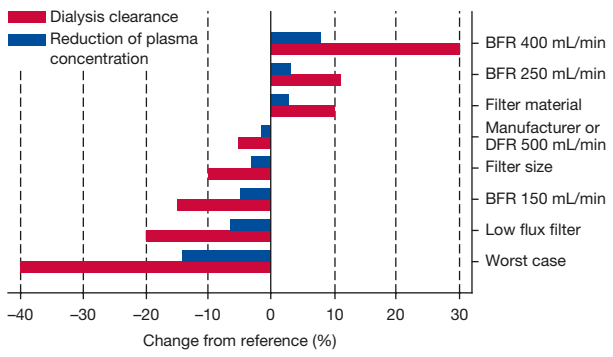
Parameter	Value	RSE (%)	Description
Fixed effects			
CL/F[a] (L/h)	12.4	28.71	Total body clearance (renal and non-renal)
V_2/F (L)	531	22.60	Volume of distribution of central compartment
Q/F (L/h)	152	14.34	Intercompartmental clearance
V_3/F (L)	499	9.42	Volume of distribution of peripheral compartment
k_a (h^{-1})	0.821	16.81	First-order absorption rate constant
ALAG (h)	1.67	4.56	Absorption lag time
$ALAG_{3rd}$ (h)	0[b]	-	Absorption lag time of the third dose (fasted)
F	1.00[b]	-	Relative bioavailability
$EC_{50\ food\ time}$[c] (h)	0.556	11.13	Time between dose administration and food intake at which the effect on bioavailability is half of the maximum effect
$F_{min\ food\ time}$[c]	0[b]	-	Minimum bioavailability when time between dose administration and food intake is 0 (fixed to 0 due to limited data)
$Hill_{food\ time}$[c]	6.10	48.52	Hill factor describing the steepness of the relation between time to food intake and the relative bioavailability
K_oA[d] (mL/min)	313	23.39	Haemodialyzer mass transfer-area coefficient
Random effects: interindividual variability (IIV) and interoccasion variability (IOV)			
IIV CL/F (CV%)	40.4	43.01	IIV in total body clearance
IIV V_2/F (CV%)	14.3	43.07	IIV in apparent volume of distribution of central compartment
IOV k_a (CV%)	64.0	30.24	IOV in relative first-order absorption rate constant
IOV F (CV%)	48.0	26.91	IOV in relative bioavailability
Random effects: residual variability			
PRV (CV%)	8.5	24.00	Proportional residual variability

[a]$CL_{total}/F = CL_{dialysis}/F + \theta_{CL/F} \times EXP(\eta CL)$. [b]Parameters fixed.
[c]$F_{3rd\ dose} = (\theta_{Fmin\ food\ time} + (1 - \theta_{Fmin\ food\ time}) \times food\ time^{**}\theta_{Hill\ food\ time} / (\theta_{EC50\ food\ time}{}^{**}\theta_{Hill\ food\ time} + food\ time^{**}\theta_{Hill\ food\ time})) \times EXP(\kappa F)$.
[d]$CL_{dialysis}/F = BFR \times (EXP(\theta_{KoA}/BFR \times (1 - BFR/DFR)) - 1)/(EXP(\theta_{KoA}/BFR \times (1 - BFR/DFR)) - BFR/DFR)$.
BFR, blood flow rate (mL/min); $CL_{dialysis}$/F, apparent dabigatran dialysis clearance; CL_{total}/F, total apparent dabigatran clearance; CV, coefficient of variation; DFR, dialysate flow rate (mL/min); $F_{3rd\ dose}$, relative bioavailability of the third dose in each period; RSE, relative standard error; η, symbol for interindividual variability; κ, symbol for interoccasion variability; θ, symbol for fixed-effect parameter estimate.

Simulations

- Simulations of various haemodialysis settings (e.g., type of filter, dialysis flow rate and blood flow rate) led to small individual changes in plasma dabigatran concentration (–7 to +8%) (Figure 3).

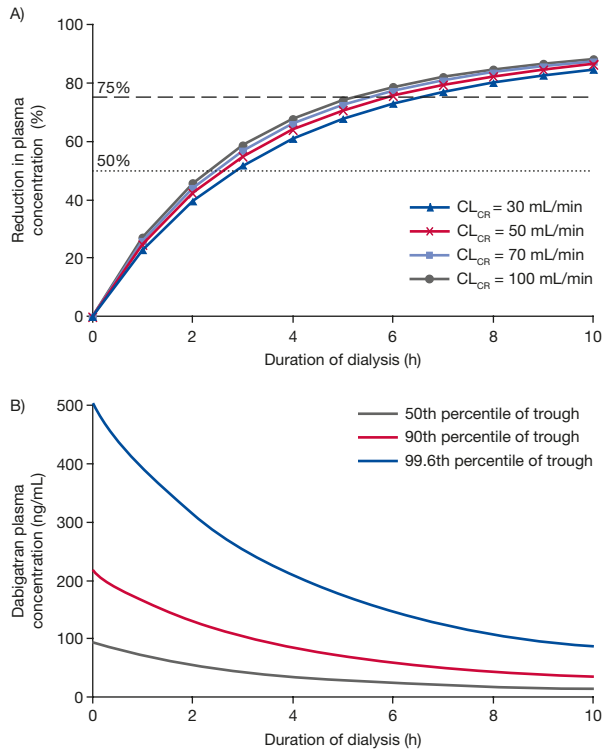
Figure 3: Simulated changes in dialysis clearance and the resulting changes in reduction in plasma dabigatran concentration for various dialysis settings compared to the reference



Reference settings: BFR, blood flow rate = 200 mL/min; DFR, dialysis flow rate = 700 mL/min; filter = large surface, high flux (Gambro PF-210H).

- The effects of changes in residual renal function were also small (Figure 4A).
- Dialysis duration had the strongest impact on the elimination of dabigatran. Plasma concentrations were roughly halved every 4 hours under dialysis (Figures 4A, B).

Figure 4: A) Predicted reduction in plasma dabigatran concentration vs duration of dialysis for patients according to renal function. B) Predicted plasma dabigatran concentration vs duration of dialysis for three different initial dabigatran concentrations*



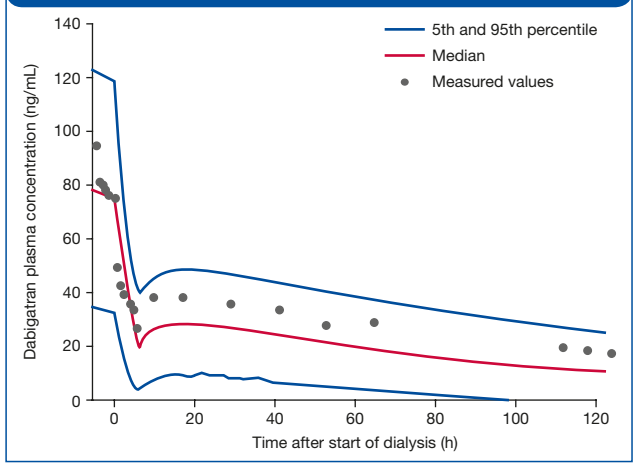
*Median, 90th and 99.6th percentiles of the trough concentrations observed in the 150 mg bid dose group in RE-LY®.
CL_{CR}, creatinine clearance.

- The average redistribution effect after dialysis was low when plasma concentrations were similar to those usually observed in AF patients.

Model Evaluation

- The final model successfully predicted the measured plasma dabigatran concentrations described in a published case report of a patient with AF undergoing dialysis for the removal of dabigatran[5] (Figure 5).
- All observed concentrations were within the 90% prediction interval.

Figure 5: Prediction of the time profile of plasma dabigatran concentrations measured in a patient undergoing haemodialysis[5]



CONCLUSIONS

- The PK model accounts for a complex interplay of dialysis factors on the PK of dabigatran. The model developed allows plasma concentration predictions under various dialysis conditions.
- Dialysis duration was identified as having the strongest impact on the reduction of plasma dabigatran concentrations.
- Redistribution effects were found to be low, however, additional real-world data are required to determine whether this will always be the case.
- The developed model might serve as a useful tool to provide guidance for optimizing the use of haemodialysis in patients where accelerated dabigatran elimination is needed, but further data from patients undergoing dialysis are needed to better evaluate the utility of this model.

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The results presented in this poster have recently been published in full: Liesenfeld KH, et al. *Clin Pharmacokinet* 2013 Mar 26. [Epub ahead of print].

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