Modelling and Simulation to Optimize the Study Design Investigating the Haemodialysis of Dabigatran in Patients With End Stage Renal Disease (ESRD)

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BACKGROUND and OBJECTIVES

- Dabigatran etexilate (DE) is an orally absorbed prodrug of dabigatran, a new thrombin inhibitor[1] that is approved for the prevention of venous thromboembolism in patients undergoing hip or knee replacement surgery and for the prevention of stroke in patients with atrial fibrillation (AF). Dabigatran is eliminated mainly unchanged (80–85% of the dose) and partially as the glucuronide (about 20%) via renal glomerular filtration.
- The objective was to use pharmacokinetic (PK) modelling and simulation to determine the optimal design of a study intended to investigate the influence of haemodialysis on the steady-state exposure of dabigatran in end stage renal disease (ESRD) patients. As redistribution of dabigatran after the end of haemodialysis may result in a clinically relevant increase in plasma concentrations, the proposed study design should allow a comprehensive investigation of this effect.

METHODS

- A PK model (including dialysis clearance) was developed based on a population PK model of a phase III study in patients with AF[2] and on information from a dedicated phase I study where dabigatran was administered as a single dose to ESRD subjects undergoing haemodialysis.[3]
  - Simulations were performed to obtain a dosing schedule for ESRD patients that results in about the same steady-state trough concentrations as in the phase III AF patient population (~90 ng/mL) within 3 days (the inter-dialysis period).
  - The impacts of three conditions were simulated to assess their influence on exposure and on the extent of redistribution:
    - Start of haemodialysis relative to intake of dabigatran etexilate (1–10 hours [h])
    - Dialysis clearance (100–300 mL/min, with an assumed bioavailability of 6% this corresponds to an apparent dialysis clearance of 100–300 L/h)
    - Dialysis duration (1–8 h).
  - The study design and sampling points were refined based on the simulation results from the proceeding step.
- Data analysis and simulations were performed using non-linear mixed-effects modelling techniques in the NONMEM® software package (version VI). Descriptive statistics and graphical visualization of NONMEM® results and simulations were performed using SAS (version 9.2) software.

RESULTS

PK Model

- A two-compartment disposition model with first-order absorption and lag time was applied. Parameter estimates used for the simulation are shown in Table 1. In ESRD patients, a remaining apparent first-order elimination rate of 20 L/h was assumed. In addition, a switchable first-order apparent dialysis clearance varying between 100 and 300 L/h was incorporated.

Simulation

- Based on the prolonged terminal half-life of dabigatran in ESRD patients and the limited time between two periods of haemodialysis (3 days), a steady-state trough concentration of ~90 ng/mL could best be obtained by a dosing schedule of DE 150 mg (day 1), 110 mg (day 2) and 75 mg (day 3).
- Figures 1–3 show the impact of the three simulated haemodialysis conditions. A larger redistribution was associated with a longer duration of haemodialysis, a later start of haemodialysis and a higher value of dialysis clearance.

Table 1: PK parameters used for simulation

Parameter	Value	Description
$CL_{non\text{-}renal}/F$ [L/h]	20	Assumed apparent non-renal clearance in ESRD subjects
$CL_{dialysis}/F$ [L/h]	100-300	Range of investigated apparent dialysis clearance values
V_2/F [L]	673*	Apparent volume distribution of central compartment
Q/F [L/h]	35.5*	Apparent inter-compartmental clearance
V_3/F [L]	345*	Apparent volume distribution of peripheral compartment
KA [h^{-1}]	0.754*	First order absorption rate constant
ALAG [h]	0.634*	Absorption lag time

*Parameter estimates from a population PK model of a phase III study in patients with AF.[2]

ESRD, end stage renal disease.

Figure 1: Simulated plasma concentration time profiles for various start times of dialysis after the last administration (4 h dialysis duration; apparent dialysis clearance 200 L/h)

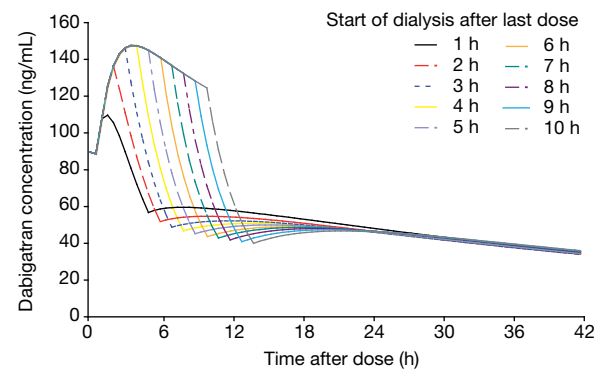


Figure 2: Simulated plasma concentration time profiles for various apparent dialysis clearances (start of dialysis 4 h after last dose; 4 h dialysis duration)

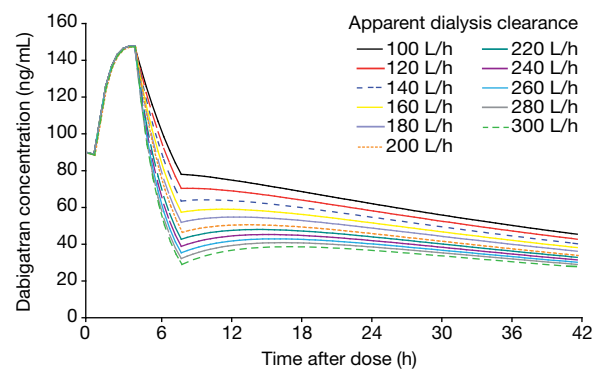
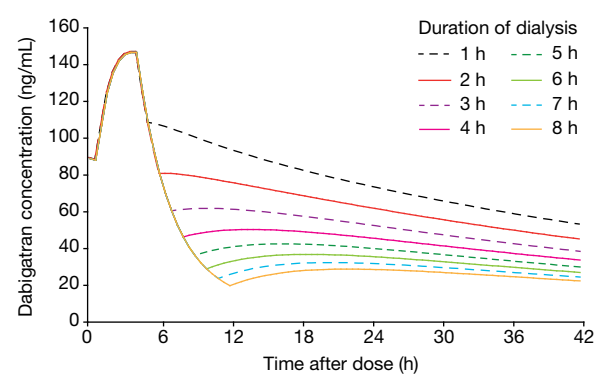


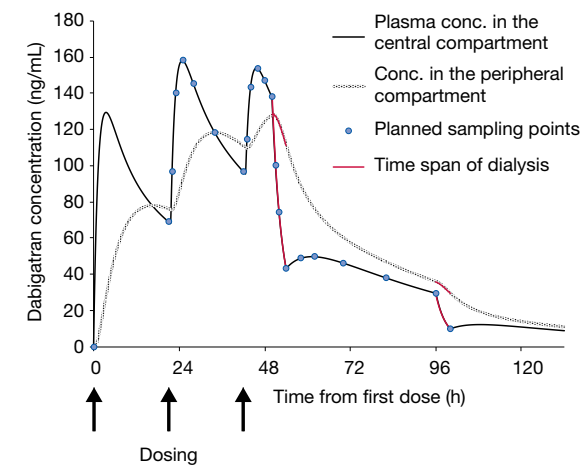
Figure 3: Simulated plasma concentration time profiles for various durations of dialysis (start of dialysis 4 h after last dose; apparent dialysis clearance 200 L/h)



Final Study Design

- For the final study design (Figure 4), a standard haemodialysis duration of 4 h was chosen.

Figure 4: Simulated concentration time profile in central (solid line) and peripheral (dashed line) compartments for a typical ESRD patient with haemodialysis (start of first dialysis 8 h after last dose; start of second dialysis 49 h after last dose; 4 h dialysis duration)



- A haemodialysis start time 8 h after the last dose was selected. This results in a redistribution effect of dabigatran close to the maximum. Nonetheless, only a relatively small absolute redistribution effect (~7 ng/mL) was predicted. The late start of haemodialysis also allows a better separation of the absorption and dialysis processes.
- For practical reasons, to allow haemodialysis and characterization of the redistribution during day-time, a shortened dosing interval of 21 h instead of 24 h was adopted in the final study design.
- Sampling points after the second dose should allow assessment of the distribution phase. Several samples after the redistribution phase are required to sufficiently investigate the remaining clearance in ESRD patients. A second dialysis at day 5 as standard procedure for ESRD patients allowed an additional sampling point.

CONCLUSIONS

- Once-daily dosing of DE for 3 days should result in central and peripheral compartment concentrations of dabigatran similar to steady-state concentrations in AF patient populations.
- Informed by the simulation results, the study design consists of a haemodialysis duration of 4 h, which should result in a sufficient reduction of the dabigatran concentration (60–75% of the initial value assuming dialysis clearance values of 160–240 mL/min) and thus allow a precise estimation of the dialysis clearance.
- The start of dialysis 8 h after the last dose should result in the maximum redistribution effect and allow an estimation of dialysis clearance variability.

REFERENCES

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