Pharmacokinetic/pharmacodynamic model for unfractionated heparin dosing during cardiopulmonary bypass

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Abstract

Background. High-dose heparin is used during cardiopulmonary bypass (CPB) to prevent thrombosis in the circuits used for extracorporeal circulation. The aim of this study was, initially, to develop a population pharmacokinetic/pharmacodynamic (PK/PD) model to assess the variability of PK/PD parameters and their correlation with the results of the routine haemostatic test activated clotting time (ACT) and thereafter to develop a Bayesian estimator enabling an individualized dosing strategy.

Methods. Fifty consecutive patients undergoing cardiac surgery with CPB were included in the study. Heparin was administered as an initial bolus of 300 IU kg⁻¹ followed by additional boluses of 5000 IU to maintain ACT < 400 s. In total, 361 blood samples were collected. The PK and PD data were analysed using a non-linear mixed effect model.

Results. A two-compartment model with a linear elimination link to an $E_{\text{max}}$ model best described heparin anti-factor Xa activities and ACT. Covariate analysis showed that body weight was positively correlated with clearance and central compartment volume. Inclusion of body weight with these parameters decreased their variability by 11 and 15%, respectively. The Bayesian estimator performed well in predicting individual parameters in an independent group of patients.

Conclusions. A population PK/PD analysis of heparin during CPB, using a routine haemostatic test, shows that Bayesian estimation might help to predict ACT on the basis of only one or two blood samples.

Key words: blood coagulation tests; heparin; cardiopulmonary bypass models; biological hemostatics

Unfractionated heparin (UFH) is used for the prevention and treatment of thrombotic events. It comprises a mixture of polysaccharides with a molecular weight ranging from 3000 to 30 000 Da. It produces its major anticoagulant effect by inactivating thrombin and activated factor X through an antithrombin-dependent mechanism.¹ Owing to the substantial pharmacokinetic (PK) and pharmacodynamic (PD) variability of UFH, the extent of its anticoagulant effect is unpredictable.² During cardiopulmonary bypass (CPB), high-dose heparin (300-400 IU kg⁻¹) is needed to prevent thrombosis in the circuits.
Editor’s key points

- Variability in the anticoagulant effect of empirically administered heparin requires measurement using point-of-care clotting assays.
- Simultaneous measurements of heparin pharmacokinetics (anti-factor Xa activity) and pharmacodynamics (activated clotting time) were used to develop a population-based model.
- The model predicted individual parameters in a test set and in simulations, but requires validation in a large cohort.

Methods

Patients

This was a prospective, observational, routine medical care clinical study, in which 50 consecutive patients were included. The study was approved by the regional ethics committee (Institutional Review Board number: IRBN012016/CHUSTE). The requirement for written informed consent was waived by the ethics committee on the grounds that the study did not necessitate any supplementary surgical procedure or laboratory samples compared with standard care. All patients underwent cardiac surgery involving CPB at the University Hospital of Saint-Etienne from February to April 2016.

Treatment procedure

Anesthesia was induced according to the standard protocol used in CPB. Non-heparin-coated bypass circuits (LivaNova group PVC, Clamart, France) including an integrated phosphorylcholine-coated oxygenator system (Inspire 8F; LivaNova) were used. No centrifugal pump or closed system was used. Surgery was executed with normothermic CPB using blood cardioplegia or a cardioplegic solution (Custodiol; Eusa Pharma, Limonest, France) for myocardial protection. A non-pulsatile flow rate between 2.0 and 2.4 litres min⁻¹ m⁻² was maintained for CPB. The total priming volume for the bypass circuit was 1500 ml, consisting of 500 ml hydroxyethyl starch solution (Voluven⁶, Fresenius kabi, France) and 1000 ml crystalloid solution. An intraoperative cell salvage device (Cell Saver; Haemonetics, Limonest, France) was used in all instances. Red blood cell concentrates were transfused to maintain a haematocrit of 25–30% during CPB. Fresh-frozen plasma, platelet concentrates, and fibrinogen concentrate were administered according to institutional standards. Anticoagulation during CPB was managed with an initial bolus of heparin of 300 IU kg⁻¹ (Panpharma, Fougeres, France) with additional boluses of 5000 IU as needed to maintain an ACT >400 s. Heparin anticoagulation was antagonized with protamine sulphate, at a dose necessary to reach an ACT close (within 10%) to the initial value recorded before heparin administration.

Biological sample collection and analysis

The ACT was measured at baseline (before administration of heparin) and then regularly during surgery using a Hemochron Junior2 ACT kit (International Technidyne, Edison, NJ, USA). For PK analysis, 5 ml samples of venous blood were drawn into citrated tubes at the time of each ACT measurement. Anti-factor Xa activities of heparin were determined on a BCS analyser (Siemens, Saint-Denis, France), using a chromogenic substrate assay (BIOPHEN⁷ Heparin; Hyphen BioMed, Neuville sur Oise, France). Heparin concentration was expressed as anti-factor Xa activity (in international units per millilitre) compared with an internal standard. The calibration curve ranged from 0 to 1.55 IU ml⁻¹. Plasma samples outside the quantification range of the assay (>1.55 IU ml⁻¹) were automatically prediluted to 1:5 or even 1:10 with pooled normal human platelet-poor plasma. The lower limit of quantification was 0.05 IU ml⁻¹.

Pharmacokinetic/pharmacodynamic model development

Heparin anti-factor Xa activities (PK) and ACT values (PD) were analysed jointly using the following non-linear mixed-effect model framework:

\[
\begin{align*}
\text{aXa}_i &= C(t_i, f_i) + (\alpha_{PK} + b_{PK} \times C(t_i, f_i)) \times e_{PK}^i \\
\text{ACT}_i &= E(t_i, f_i) + (\alpha_{PD} + b_{PD} \times E(t_i, f_i)) \times e_{PD}^i
\end{align*}
\]

where \(\text{aXa}_i\) and \(\text{ACT}_i\) are the observed anti-factor Xa activity and ACT, respectively, for patient \(i\) at time \(j\). The functions \(C(t, f)\) and \(E(t, f)\) correspond, respectively, to anti-factor Xa activity and the ACT returned by the models for patient \(i\) at time \(j\) with the individual parameters \(f\). Parameters \(\alpha_{PK}, \alpha_{PD}, b_{PK}, \) and \(b_{PD}\) are the constant and proportional parts of the error model for PK and PD with \(e_{PK}^i \sim N(0,1)\) and \(e_{PD}^i \sim N(0,1)\).

For the PK model, different structures (one and two compartments) and elimination processes (linear and Michaelis–Menten) were tested. For the PK/PD relationship, a linear model and an \(E_{\text{max}}\) model were tested. Individual parameters were assumed to be log-normally distributed. The covariates were included in the model using a stepwise method with forward inclusion and backward elimination. All continuous covariates were logarithmically transformed and scaled to a typical value; for example, the effect of body weight on the parameter \(V_{CI}\) was evaluated as follows:
log(Vc) = Vc + b^{bw} \times \log \left( \frac{BW}{70} \right) + W^{ci}

where \(Vc\), \(BW\), and \(W^{ci}\) denote the volume of distribution, body weight, and random effect of patient \(i\), respectively. The parameter \(b^{bw}\) corresponds to the regression coefficient of body weight of \(Vc\).

Data were analysed using MONOLIX\textsuperscript{8} non-linear mixed effects modelling software (Lixoft, version 4.3.2)\textsuperscript{10} with the SAEM algorithm.\textsuperscript{11} Data below the lower limit of quantification were left censored.\textsuperscript{12} All graphics were generated using the ggplot2 software package\textsuperscript{13} with R software.\textsuperscript{14}

Model evaluation and selection were based on visual inspection of the goodness-of-fit plots, the precision of parameter estimates, and the decrease in objective function (calculated by importance sampling).\textsuperscript{15} The goodness of fit was established by plotting the population predictions of the model vs observations, the individual predictions vs observations, and the normalized prediction distribution errors (NPDEs) vs time. The prediction-corrected visual predictive check (PC VPC)\textsuperscript{15} was generated by simulating individual PK parameters 1000 times. The ability of the model to describe the observations was evaluated by inspection of the distribution of the simulated concentrations. The median parameter values and the 90% prediction interval of the VPC replicates were compared with the observations composing the original data set.

Evaluation of model predictiveness

For three randomly selected patients not used for estimation of the population PK/PD model, individual parameters were estimated by the maximum a posteriori probability method using the population PK/PD model previously developed. Individual parameters were estimated using the following three different data sets: (i) only the first ACT measurement after heparin administration; (ii) only the first two ACT measurements after heparin administration; and (iii) all available anti-factor Xa activities and ACT measurements. Individual parameters of these subjects were estimated using the maximum a posteriori probability method, using the population PK/PD model previously estimated.\textsuperscript{16} This approach has been used to forecast intraoperative plasma concentrations of alfentanil.\textsuperscript{17}

The quantity of protamine needed was also calculated using the model and compared with the first empirically based dose administered. The protamine requirement estimated by the model was based on the hypothesis of a 1:1 ratio between the quantities of heparin in the central and peripheral compartments, as estimated by the model, at the end of surgery.

Results

Patients and biological samples

All subjects (50/50) were included in the PK/PD analyses. Patient and heparin treatment characteristics are described in Table 1. The median number of heparin boluses administered was 4 (1–8), and the median total amount of heparin was 35 000 (20 000–55 000) IU.

A total of 361 blood samples were drawn, permitting 361 anti-factor Xa activities and 341 ACT measurements. The mean (range) values per patient were 7.2 (3–12) IU ml for anti-factor Xa activity and 6.8 (3–13) s for ACT.

Population pharmacokinetic model of unfractionated heparin

A two-compartment model with linear elimination best described heparin anti-factor Xa activities, as follows:

\[
\frac{dC_c}{dt} = \text{input}(t) + Q \left( \frac{C_p}{V_p} \right) \frac{C_c}{V_c} + \frac{CI}{V_c} \times C_c
\]

\[
\frac{dC_p}{dt} = Q \left( \frac{C_c}{V_c} \right) \frac{C_p}{V_p} + \text{input}(t) = \text{Dose}_i \left( \frac{C_p}{V_c} \right) \text{ if } t = t_i \text{ (d > 1)}
\]

\[
C_c = \frac{\text{Dose}_i}{V_c} \text{ and } C_p(0) = 0
\]

where \(C_c\) and \(C_p\) are the anti-factor Xa activities in the central and peripheral compartments, respectively. The parameters \(V_c\), \(V_p\), \(Q\), and \(CI\) represent the central volume of distribution, the peripheral volume of distribution, the intercompartmental clearance, and the elimination clearance, respectively.

A proportional model best described residual variability. No relevant inter-individual variability was detected for parameters \(Q\) and \(V_c\). Among the continuous (age, body weight, glomerular filtration rate) and categorical (sex, ASA physical status) covariates evaluated, body weight had a statistically significant effect on \(Cl\). The regres-

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Population pharmacokinetic/pharmacodynamic model of activated clotting time

The best PK/PD model corresponded to an $E_{\text{max}}$ relationship between anti-factor Xa activities and its anticoagulant effect based on ACT, implemented as follows:

$$\text{ACT} = \text{ACT}_0 + \frac{E_{\text{max}} \times C_x}{C_{50} + C_x}$$

where the parameters $\text{ACT}_0$, $E_{\text{max}}$, and $C_{50}$ represent the baseline ACT value, maximal response value, and anti-factor Xa activity producing 50% of the maximal response value, respectively. As the Hemochron Junior ACT kit has an upper limit of quantification of 1000 s, the parameter $E_{\text{max}}$ was considered to follow a logit-normal distribution for values between 0 and 1000 s. A proportional model best described the residual variability of ACT. No clinically relevant inter-individual variability was detected for the parameter $C_{50}$. None of the continuous or categorical covariates significantly affected PD parameters. Estimates of population PD parameters are presented in Table 2.

Model evaluation

The goodness-of-fit plots of the final model are shown in Fig. 1. The data exhibited no apparent bias in model prediction. Figure 2 represents the VPC of the PK/PD relationship. This indicates a good overall predictive capacity of the model, with ACT

### Table 2

Estimates of population parameters. $\text{ACT}_0$, baseline ACT value; $C_{50}$, anti-factor Xa activity that produces 50% of the maximal response value; $C_l$, UFH elimination clearance; $E_{\text{max}}$, maximal response value; PD, pharmacodynamic; PK, pharmacokinetic; $Q$, UFH intercompartmental clearance; $\sigma_{\text{PD,proportional}}$, proportional residual variability for PD; $\sigma_{\text{PK,proportional}}$, proportional residual variability for PK; UFH, unfractionated heparin; $V_C$, volume of distribution of the central compartment; $V_P$, volume of distribution of the peripheral compartment; RSE, relative standard error.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Population mean (% RSE)</th>
<th>Interpatient variability (% RSE)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PK parameters</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$V_C$ (litres)</td>
<td>3.1 (4)</td>
<td>0.119 (18)</td>
</tr>
<tr>
<td>$V_P$ (litres)</td>
<td>2.23 (8)</td>
<td>—</td>
</tr>
<tr>
<td>$Q$ (litres h$^{-1}$)</td>
<td>4.67 (15)</td>
<td>—</td>
</tr>
<tr>
<td>$C_l$ (litres h$^{-1}$)</td>
<td>0.841 (10)</td>
<td>0.221 (20)</td>
</tr>
<tr>
<td><strong>Covariate parameters</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ln(Weight/70) on $V_C$</td>
<td>1 (fixed)</td>
<td>—</td>
</tr>
<tr>
<td>ln(Weight/70) on $C_l$</td>
<td>0.767 (29)</td>
<td>—</td>
</tr>
<tr>
<td><strong>PD parameters</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\text{ACT}_0$ (s)</td>
<td>116 (3)</td>
<td>0.104 (31)</td>
</tr>
<tr>
<td>$C_{50}$ (IU ml$^{-1}$)</td>
<td>3.49 (13)</td>
<td>—</td>
</tr>
<tr>
<td>$E_{\text{max}}$ (s)</td>
<td>720 (5)</td>
<td>0.419 (14)</td>
</tr>
<tr>
<td><strong>Residual error parameters</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\sigma_{\text{PD,proportional}}$</td>
<td>0.0993 (6)</td>
<td>—</td>
</tr>
<tr>
<td>$\sigma_{\text{PK,proportional}}$</td>
<td>0.14 (5)</td>
<td>—</td>
</tr>
</tbody>
</table>
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values above the 90th quantile of the simulations corresponding to aberrant ACT measurements.

Simulation and assessment of model predictiveness

Figure 3 presents simulations based on the population model for two different heparin administration strategies: (i) an initial bolus of 350 IU kg\(^{-1}\) plus additional boluses of 5000 IU every hour; and (ii) one bolus of 300 IU kg\(^{-1}\) followed by an infusion of 55 IU kg\(^{-1}\) h\(^{-1}\) for a patient weighing 70 kg. The infusion-based strategy allowed control of the ACT within the first 0.5 h and also reduced ACT variability.

Predictions of ACT profiles for the three patients whose data were not used for the population model estimation are shown in Fig. 4. These profiles indicate that the population model (black curve) predicted ACT values of each patient reasonably well. Models based on individual parameters, estimated using only the first (green curves) and the first two (blue curves) ACT values, predicted ACT during surgery even better. These curves are very close to the orange curves, corresponding to the estimated individual model based on all available anti-factor Xa activities and ACT values. Predictions of ACT and anti-factor Xa activity for a patient with heparin resistance and for a patient with a high level of haemodilution (patients included when building the model) are presented in supplementary data Fig. S1 and illustrate the good predictions by the model for such difficult patients.

Predictions of the required quantity of protamine estimated by the model are presented in Table 1. The ratio between the median first protamine dose administered and estimated protamine requirement was 0.86 (minimum–0.59, maximum–1.44).

Discussion

In most types of cardiac surgery, an empirical heparin dosing regimen is implemented, starting with a bolus of 300–400 IU kg\(^{-1}\) and continuing with additional 5000 IU boluses to maintain the anticoagulant effect. Heparin monitoring during surgery is based on either a functional test of anticoagulation or quantitative measurements of the concentration of circulating heparin.\(^{19}\) The ACT is most widely used to measure heparin anticoagulation in the operating theatre. For most anaesthesia teams, the target ACT value before starting CPB ranges from 400 to 480 s.\(^{20}\) In the present study, all patients maintained an ACT >400 s. However, 20% had ACT values >600 s, which carries a risk of over-anticoagulation and bleeding events. Moreover, in some situations, ACT measurements are inaccurate with respect to heparin concentrations.\(^{19}\) Adjustment of dosing regimens on the basis of these biased values of ACT could lead to inappropriate dosage adjustment (under- or overdosing), increased monitoring frequency, and greater PK/PD variability. A model-based approach taking into account inter- and intra-individual PK/PD variability might therefore improve dose adjustment.\(^{21}\)

This study is the first to describe the PK/PD of heparin using routine tests in patients undergoing CPB. Anti-factor Xa activity was used to monitor heparin PK because it represents the amount of heparin in the blood and not necessarily antithrombotic function. Pharmacodynamic profiles were evaluated using ACT, the coagulation test most widely used in the operating theatre. Analyses showed that the PK/PD parameters of i.v. heparin were adequately described by a two-compartment model with first-order elimination linked to an \(E_{\max}\) model. In a previous study, Jia and colleagues\(^{22}\) described the pharmacokinetics of heparin in a similar population using an anti-factor IIa reagent, which is not a useful test for monitoring heparin anticoagulant activities. Anti-factor IIa activity was also well described by a bi-compartmental model with linear elimination, and the population PK parameters returned by the two models were similar. The central volume of distribution and elimination half-life were estimated to be 3.1 litres and 153 min, respectively, in our study, compared with 3.0 litres and 107 min in the study by Jia and colleagues.\(^{22}\) The inter-individual variability of PK parameters was substantial, being initially estimated (in terms of % coefficient of variation (CV)) to be 33% for Cl and 27% for \(V_C\). These estimates are similar to those reported by Jia and colleagues\(^{22}\) (35% for Cl and 32% for \(V_C\)). Inclusion of body weight as a covariate for \(V_C\) and Cl led to a decrease of 15 and 11%, respectively, in the inter-individual variability of these two parameters. Al-Sallami and colleagues\(^{23}\) described the pharmacokinetics and pharmacodynamics of heparin in children. In that study, the pharmacokinetics of heparin were characterized by a protamine titration assay, whereas its pharmacodynamics were evaluated on the basis of activated partial thromboplastin time. The pharmacokinetics of heparin were well described by a single-compartment model, and there was a significant relationship between body weight, volume of distribution, and elimination clearance, corroborating our findings. However, the inter-individual variability was extremely high (50% for Cl and 40% for \(V_C\)).\(^{23}\)

Anti-factor Xa activities of heparin were closely correlated with ACT, illustrating the predictability of drug exposure and suggesting that ACT is an appropriate test for measuring heparin exposure and effect on coagulation. The model corresponds to an \(E_{\max}\) relationship between anti-factor Xa activities and ACT. Although most previously published studies describe this relationship as linear, the \(E_{\max}\) model is more physiological.
Notably, the wide range of anti-factor Xa and ACT values observed allowed precise estimation of this relationship. The VPC for the PK/PD relationship showed good agreement between simulated and observed ACT values. Some falsely elevated ACT values were measured. These values were inconsistent with the anti-factor Xa activity measured at the same time. This discrepancy is a known phenomenon observed with use of a point-of-care device to determine ACT.\textsuperscript{19} Assessment of the PK/PD relationship and its variability enabled the proposed model to be robust against such aberrant ACT values, as illustrated in Fig. 4. Jia and colleagues\textsuperscript{22} did not link anti-factor IIa activity to a pharmacodynamic parameter evaluating heparin anticoagulant function, reducing the practical value of their study, because rapid direct measurement of anti-factor IIa activity is not feasible in the operating theatre.

The final PK/PD model allowed performance of simulations to evaluate variability. The overall variability of PK/PD parameters remained substantial, with the simulation demonstrating a wide range of predicted values for both anti-factor Xa activities and ACT. Dose adjustment based on body weight is therefore not sufficient, and the use of monitoring is warranted. Moreover, simulations demonstrate that administration of multiple boluses of heparin is not an effective way of maintaining ACT $>400$ s even in the context of short surgical interventions. A bolus-plus-infusion regimen allows more rapid achievement of the target concentration (within 30 min), limiting maximal ACT while restricting variability.

Use of Bayesian estimators requiring only one or two ACT measurements could provide a fast and accurate alternative means of estimating specific individual PK/PD parameters and allowing personalized heparin dose adjustment. This approach could also be used to improve protamine administration strategies. At present, protamine administration is empirically based on the total dose of heparin, the duration of CBP, and the last ACT value. Based on the hypothesis of a 1:1 ratio between heparin and protamine, our model was able to estimate the amount of protamine to be administered at the end of surgery. The ratio between the median first protamine dose administered and the estimated protamine requirement was 0.86. This value seems to be in accordance with those reported in other studies.\textsuperscript{24–26} However, 30% of patients in the present study received a second dose of protamine. The optimal protamine:heparin ratio and
optimal mode of protamine administration warrant further investigation.

One limitation of this model is that ACTs measured by different devices are not directly comparable. However, it is easy to overcome this problem by modifying the residual error in the model on the basis of the analytical information provided by the manufacturers of the devices concerned. A second limitation is its small size, precluding specific evaluation, as a covariate effect, of the impact of difficult situations (heparin resistance, haemodilution, hypothermia, inflammatory process) that could impact the heparin dosing regimen. However, the reliability of the model remains good in these situations (see supplementary data). Moreover, the aim of this study was to develop a general model that does not depend on too many specific situations. Ultimately, this work needs to be validated prospectively in a large cohort of patients to demonstrate its ability to tailor heparin administration strategy.

In conclusion, we propose a PK/PD model of heparin for patients undergoing cardiac surgery with CPB. Body weight appears to influence heparin disposition and elimination. However, inter-individual variability of PK/PD parameters remains high. Point-of-care instruments could facilitate monitoring the antithrombotic effect of heparin and also allow estimation of the circulating concentration of heparin during cardiac surgery. In addition, algorithms could be implemented to determine the initial dosing regimen and facilitate selection of an optimal dosing regimen on the basis of one or two ACT measurements.

Supplementary material
Supplementary material is available at British Journal of Anaesthesia online.

Declaration of interest
None declared.

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Authors’ contributions
Study design/planning: L.G., X.D., P.M., S.C.
Data analysis: X.D., E.O., S.H., A.M.
Writing of manuscript: X.D., E.O., L.G., S.C.
Revision and final approval of manuscript: all authors.
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