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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_{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

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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.

used for extracorporeal circulation. Monitoring the level of heparin-induced anticoagulation is therefore crucial, especially in the context of high blood heparin concentrations when standard coagulation tests (activated partial thromboplastin time or anti-factor Xa assay) cannot be used. The activated clotting time (ACT) has served as the clinical standard for determining the adequacy of heparin administration and its reversal in the operating theatre.[3–5] In most instances, heparin dosing based on a single ACT measurement is sufficient for full anticoagulation. However, in some clinical situations (such as heparin resistance, haemodilution, and hypothermia) ACT is of more limited value, and discrepancies between heparin dose, heparin effect, and heparin concentration have been observed.[6–9] Although many other devices are available to assess individual heparin sensitivity, ACT remains the most commonly used functional test.

The aim of this study was, initially, to develop a PK/PD model using standard assays to evaluate the variability of heparin effect and the correlation between quantitative and functional tests in patients undergoing CPB and thereafter to develop a Bayesian estimator to determine individual dosing strategy based on a limited blood sampling strategy for ACT measurement.

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

Anaesthesia 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 (Voluven®, 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, Fougères, 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 (BIOPHEN® 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:

$$\begin{cases} aXa_{i,j} = C(t_{i,j},f_i) + (a_{PK} + b_{PK} \times C(t_{i,j},f_i)) \times e_{i,j}^{PK} \\ ACT_{i,j} = E(t_{i,j},f_i) + (a_{PD} + b_{PD} \times E(t_{i,j},f_i)) \times e_{i,j}^{PD} \end{cases}$$

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

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_{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_C was evaluated as follows: