Hypothesis for a partially non urinary elimination of tranexamic acid in haemorrhagic caesarean section: traces pilot pharmacokinetic study: pharmacokinetics of tranexamic acid in obstetrics

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Hypothesis for a partially non urinary elimination of tranexamic acid in haemorrhagic caesarean section: TRACES pilot pharmacokinetic study

Short title: Pharmacokinetics of tranexamic acid in obstetrics

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Abstract

Background

In previous studies, the choice of doses of tranexamic acid was empirically defined as no pharmacokinetic study had been conducted in haemorrhagic caesarean section.

Objective

The objective was to build a pharmacokinetic model in patients receiving a single 0.5, 1 or 2 g intravenous bolus.

Method

A preliminary monocentric open study was performed in the Lille centre. Blood samples and one urinary sample were collected in the 6 hours following the injection. Nine patients were included. Tranexamic acid concentration was measured using liquid chromatography system coupled with tandem mass spectrometry. We used Monolix 2019R1 for population pharmacokinetic modelling. A structural model was constructed followed by the investigation of potential covariates.

Results

Data were best described with a two-compartment model with a double first-order elimination from the central compartment. The model was improved when the variable ideal weight per dose was affected as a covariate for the apparent volume of distribution. Assuming a dose of 1 g and a height of 160 cm, the pharmacokinetic parameters were estimated at 10.26 $L.h^{-1}$ for total clearance, 11.5 L for the volume of the central compartment, 15.8 L for the volume of the second compartment, a diffusional clearance of 30.36 $L.h^{-1}$, and a urinary excretion fraction of 25.8%.

Conclusions

The population pharmacokinetic model of tranexamic acid in haemorrhagic caesarean section was successfully established in our tiny sample of patients. The results of this preliminary TRACES pharmacokinetic study suggested that elimination of tranexamic acid is partially non urinary in contrast with healthy patients.

Keywords: caesarean section; intravenous; pharmacokinetics; postpartum haemorrhage; tranexamic acid.

Main text

1. Introduction

Primary postpartum haemorrhage (PPH) refers to an estimated blood loss of more than 500 mL after vaginal birth or 1000 mL after caesarean section within 24 hours of giving birth. In 2010, PPH was responsible for 27% of maternal death worldwide placing it at the head of the causes of maternal death (Say et al., 2014).

Tranexamic acid (TA) prevents bleeding by inhibiting the enzymatic breakdown of fibrin blood clots. This molecular analogue of lysine inhibits fibrinolysis by reducing the binding of plasminogen and t-PA to fibrin.

Previous findings showed that TA improved prognosis through reduction of death due to bleeding in surgery, trauma and PPH with various uniform dose regimen. The CRASH-2 trial proposed a loading dose of 1 g over 10 min followed by an infusion of 1g over 8 hours in trauma adults ("Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial," 2010). Then, the EXADELI trial suggested a loading dose 4 g over 1 hour, followed by an infusion of 1 g/hour over 6 hours to evaluate the impact of TA on the blood loss volume and duration in women with PPH (Ducloy-Bouthors et al., 2011). Finally, the WOMAN Trial randomly recently assigned patients to receive TA 1 g intravenously (followed by a second if bleeding continued after 30 min or restarted within 24 hours) or matching placebo with successful results on the reduction of death due to bleeding in the treated group (Shakur et al., 2017). Based on those studies, WHO strongly recommends early use of intravenous tranexamic acid (within 3 h of birth) with an intravenous dose of 1 g over 10 min, followed by a second dose of 1 g if bleeding continues after 30 min or restarts within 24 h of completing the first dose (Vogel et al., 2018). The 1 g and 4 g dose regimen chosen in the EXADELI and WOMAN trials for the treatment of PPH relied on the results of studies conducted in patients with very different characteristics from parturient women**.** To investigate the best dose regimen and any need for dose adjustment in the treatment of PPH, pharmacokinetic (PK) studies are required. Until today, no PK studies for TA in the treatment of PPH have been held in literature. Contrary to common believes, TA have several mechanisms of action to be explored. In fact, plasmin-induced platelet activation and intrinsic generation of thrombin through activation of factor XII (Soslau et al., 1991; Stief, 2012, 2009) were proposed to explain its efficacy in acute haemorrhage. Parallel analysis of blood loss, TA concentration and fibrinolysis inhibition have never been performed in vivo in haemorrhagic caesarean section. Pharmacodynamic pharmacokinetic (PK-PD) study will be required. The first step will consist in the build of a PK model.

Our objective was to build a PK model in patients receiving a single 0.5, 1 or 2 g intravenous (i.v) bolus and to identify the factors most closely tied up to therapeutic variability between individuals through a PK study.

2. Methods

TRACES trial is a multicenter randomized double-blind placebo-controlled study whose target will be to evaluate the dose-ranging efficiency of TA on blood loss reduction in patients experiencing PPH during elective or non-emergent caesarean section delivery (Bouthors et al., 2018). TRACES pilot is the preliminary PK study of TRACES trial.

2.1. Ethics approval

TRACES trial was approved by the competent national authorities (ANSM 201500249926) and the Ethics Committee (CPP 15/50 020216) before beginning the study following article L1121-4 of the Public Healthcare Code. This trial has been declared on the clinical trials registration under the number CT 02797119 (Bouthors et al., 2018).

2.2. Patients and Data Collection

TRACES pilot was a monocentric open preliminary technical validation study performed over 2 months (Appendix A). Nine patients participated in the preliminary PK study (Fig. 1). Patients were included if they were undergoing haemorrhagic cesarean section (blood loss > 800 mL) and receiving a single i.v dose of TA (0.5, 1 or 2 g over 1 minute). Non-inclusion criteria used were presented in the TRACES pilot study protocol (Bouthors et al., 2018).

2.3. Measurements and data handling

The blood TDM samples were obtained from our patients at T0 (inclusion time, when bleeding ≥ 800 mL is diagnosed), T1 (at the end of injection), T15, T30, T60, T120, T180, and T360 (defined as 15, 30, 60, 120, 180 and 360 min after the injection). The urinary samples were collected within 6 hours after treatment.

The characteristics collected for each patient were age, body weight (BW), height, dose, TA concentration at any time from the injection to T360, serum creatinine concentration, urea, volume of intravenous fluids administered all along the study period, the loss of blood volume before inclusion (Vs1), and additional blood loss (Vs2). Urines were collected in a graduated urinary bag from the administration of TA to T360. Body surface area (BSA) (Dubois and Dubois, 871), ideal weight (IW) (Robinson et al., 1983), body mass index (BMI) where calculated. Clearance of creatinine (Clcr) was calculated thanks to Cockcroft and Gault formula. Glomerular filtration rate (GFR) was estimated with MDRD and CKD-EPI formulas. We also considered the unstability of the Clcr in this particulate and acute situation using the Jelliffe (1972) (Jelliffe and Jelliffe, 1972) and Chiou (1975) (Chiou and Hsu, 1975) computation formulas.

2.4. Sample Analysis

The sample analysis was described in the TRACES pilot study protocol (Bouthors et al., 2018). Blood and urinary samples were analyzed by the toxicology laboratory of the Lille centre.

Fifty microliters of plasma or pre-diluted (1/10th) urine were mixed and centrifuged (4500 g, 4 °C, 10 min) after addition of 400 µL of methanol containing 7β-hydroxyethyl-theophylline (Sigma-Aldrich, Saint Quentin Fallavier, France) at 20 $mg.L^{-1}$, as an internal standard. The supernatant (20 µL) was added to water/formic acid 0.1% (180 µL).

Measures were carried out on liquid chromatography system coupled with tandem mass spectrometry (Acquity Xevo-TQ Detector, Waters, Milford, MA, USA) following a fully validated method (Ducloy-Bouthors et al., 2018). The lower limit of quantification was 2 mg/L. Linearity was tested using the calibration range 5–200 mg/L (r^2 =0.995). Intra-day and interday precisions were <3.80% and 5.30%, respectively, for a 20-mg/L-spiked sample and <2.90% and 4.15%, respectively, for a 150-mg/L-spiked sample. The system was equipped with an

HSS T3 column (1.8 µm × 2.1 × 50 mm) maintained at +50°C. Compounds were separated using a mobile phase gradient consisting of methanol and formic acid. Ions of each analyzed compound were detected in a positive ion mode using multiple reaction monitoring (MRM). An injection volume of 5 µL was used for all the analyses. Data acquisition and quantification were performed using MassLynx 4.1 Software (Waters).

2.5. PK modelling

The PK parameters were estimated using the parametric NLMEM software program Monolix 2019R1 (Lixoft, Orsay, France) by applying the stochastic approximation expectation-maximization algorithm (SAEM) combined with a Markov Chain Monte Carlo procedure (Chan et al., 2011). This SAEM algorithm estimates for each patient the distribution of the fixed parameters. The fixed parameters were computed without any approximation of the model (no linearisation).

In this article, we considered NLMEMs for discrete data where the conditional probability for observation y_{ij} at sample j=1 to n_i from patient i can be written as:

$$\boldsymbol{y_{i,j} = f(t_{i,j}, \psi_{i,j}) + g(t_{i,j}, \psi_{i,j}) * \varepsilon_{i,j}}, \boldsymbol{\varepsilon_{i,j}} \sim N(0, 1)$$

Where y represents the plasmatic or urinary concentration in TA estimated at t_j for a patient i, $\boldsymbol{f}$ represents the non-linear function of the model, $t_{i,j}$ represents the time of sampling, $\boldsymbol{\psi_{i,j}}$ represents the set of PK parameters, $\boldsymbol{g}$ represents the residual error model and $\boldsymbol{\varepsilon_{i,j}}$ represents the residual error.

The expression of the log of the population PK parameter for individual i is given by:

$$\boldsymbol{log(P_i) = log\,(\theta_P) + \beta_1 * x_1 + \eta_i}\,, \boldsymbol{\eta_i} \sim N(0, \boldsymbol{\omega_P})$$

Where θ_P represents the fixed effect parameter in our population, β_1 represents the effect of covariate x_1, η_i represents the between subject variability (BSV) term on parameter P for subject i, $\boldsymbol{\omega_P}^2$ represents the variance of the interindividual error.

η_i is the realization of the random-variable η capturing the BSV. η is assumed normally distributed with variance $\boldsymbol{\omega}_P^2$.

First, we built the base model for TA using the blood and the urinary concentrations. Secondly, we evaluated the potential influence of the patients' characteristics on the TA kinetics.

Random effects of parameters were plotted against covariates to identify possible relationships between them. Covariate testing was assessed with a multiple sequential regression analysis. Only the covariates significantly correlated with at least one PK parameter with a risk of 5% were included in the final structural model for investigation. Parameters considered for covariate testing were the followings: dose, age, BW, IW, height, BMI, BSA, serum creatinine, urea, volume of intravenous fluids, Vs1, Clcr and GFR calculated using the different formulas described above. Concerning our choice of covariates, we considered anthropometric parameters, parameters measuring the renal function and coagulation parameters. In fact, many studies tested successfully anthropometric parameters as covariates of the volume of distribution of TA; renal parameters are well known to influence the elimination of drugs and were also integrated to our analysis; the Vs2 was not introduced as covariate for our model as we were looking for predictive parameters for the time course of TA concentration.

For base and covariate modelling, the PK parameters were assumed to follow a log-normal distribution. The constant, proportional, and combined error models were tested to assess the residual variability. The base and covariate models were selected according to the minimisation of the objective function value including the maximized log-likelihood (-2LL) and the corrected Bayesian information criterion (BICc) (Delattre et al., 2014; Schwarz, 1978), while ensuring that the condition index calculated from the Fisher Information Matrix is within the limits generally assumed (Gujarati, n.d.). We based our selection on the BICc which is penalized from the maximized log-likelihood by a term that depends on the number of fixed effect parameters and the sample size and which was adapted from the initial BIC for general mixed effects models. The model was accepted if the condition index was below 100. The validation of the models was assessed with (1) the precision of the parameter estimation expressed as the relative standard error (RSE, in %), the goodness of fit of each model according to diagnostic plots such as (2) the observed versus predicted concentration scatter plots, (3) the visual predictive check (VPC), and (4) the diagnostic plot for normalized prediction distribution error (NPDE) (Nguyen et al., 2017). The corrected VPC was used for this study as the doses were not the same for each patient (Bergstrand et al., 2011). The validation of a non-linear mixed-effect model is under-pinned by the precision of the estimations obtained from the bootstrap mostly which must reach the required standards (≤30% for fixed effect parameters and ≤50% for $\boldsymbol{\omega}\theta$). As we worked on a parametric software, a Shapiro Wilk test (α=5%) was computed to assess the normality of the η and $\varepsilon_{i,j}$. The graphs were computed using Monolix 2019R1.

The RSE given by monolix are computed asymptotically from the inverse of the Fisher Information Matrix. However, only 9 subjects with 7 sampling times are considered in our study, which can lead to unprecised estimation of the uncertainty. In order to obtain a more accurate estimation of the uncertainty on the fixed effect parameters, a parametric bootstrap method was performed using R software (version 3.6.1) implemented with the Rsmlx package (version 2.0.2). A bootstrap consists in repeating random sampling with replacement of the original data to create a new data set of the same size as the original but with a different combination of subjects (and their data). This resampling was repeated 1000 times. For the interpretation of our data, we considered the relative standard error (%) of the fixed and random parameters obtained from the bootstrap rather than the ones estimated from the original dataset.

2.6. PK simulations

To characterize the influence of the dose-regimen and the chosen covariates on TA kinetics, we generated PK simulations on a fictive group of 1000 individuals parametrized with individual randomization using R software (version 3.6.1) implemented with the mlxR package (version 4.0).

2.7. Correlations

A spearman correlation test (R software) between the Vs2 and the predicted maximal concentration of TA (C_{max}), the area under the curve (AUC) from 0 to 360 minutes (measured using PKAnalix, version 2019R1), the TA dose received was tested.

3. Results

3.1. Patients and Data Collection

Nine patients were recruited in the PK preliminary study (Fig. 1). The patients' baseline and PPH characteristics are presented in Appendix B. The analysis included a total of 53 TA plasma concentration data.

3.2. Population PK

3.2.1. Base model

We tested seven two-compartment models and a single three-compartment model based on previous studies. In the two-compartment models, the first compartment represented the central compartment with an elimination called A and the second compartment represented the peripheral compartment with an elimination called B. The rational to test a potential elimination from the second compartment comes from the possibility that it may represent the uterine haemorrhagic compartment. Thus, the elimination of TA in the haemorrhagic blood would be represented by an elimination from the second compartment. The tested models were distinguished by their A/B elimination couple (first order, non-linear, absent). The elimination A was assumed to be ever-present as TA concentrations where objectivize in the 6 hours urine while there was no evidence that the elimination B of TA from the peripheral compartment existed. The results for the selection of the base model are summarized in Table 1.

The proportional error model was the most adequate for evaluating interpatient and residual variability. This model is written y1 = Cc + b1*Cc * ε with y1 the predicted TA concentration in the blood, Cc the observed TA concentration in the blood and b1 the fixed factor of the proportional residual error for the blood concentration. Observed data were best described with a two-compartment model with a double first-order elimination from the central compartment and no elimination from the second compartment (Fig. 2). The model n°7 is thus considered as the final base model in the remainder of this section.

This base model was parameterized using elimination clearance (Cl), the volume of central (V1) and peripheral (V2) compartments, diffusional clearance (Q), urinary excretion fraction (p_{urine}), according to the following equations:

$$\frac{dA_1}{dt} = -(k_{non\,urine} + k_{urine}) \times A_1 - k_{12} \times A_1 + k_{21} \times A_2$$

$$\frac{dA_2}{dt} = k_{12} \times A_1 - k_{21} \times A_2$$

$$\frac{dA_u}{dt} = k_{urine} \times A_1$$

$$k_{urine} = p_{urine} \times \frac{Cl}{V_1} \;;\; k_{non\,urine} = (1 - p_{urine}) \times \frac{Cl}{V_1} \;;\; k_{12} = \frac{Q}{V_1} \;;\; k_{21} = \frac{Q}{V_2}$$

In those equations A_1 represents the amount of TA in the central compartment, A_2 represents the amount of TA in the peripheral compartment, and A_u represents the amount of TA collected in the urines.

At that step, Cl was 0.171 L.min^{-1} (or 10.36 L.h^{-1}) with RSE=10.9%, V1 was 12.3 L (RSE=20.8%), and p_{urine} was 0.26 (RSE= 13.7%). We calculated a population elimination rate ($k_{non\,urine} + k_{urine}$) of 0.84 h^{-1} (0.014 min^{-1}) and a population half-time of elimination of 0.82 h (49.87 min).

3.2.2. Covariate model

Results of covariate testing showed that dose (r^2 =0.84, p-value=4.6 10^{-3}), IW per dose (r^2 =-0.95, p-value=8.8 10^{-5}), BW at the end of pregnancy per dose (r^2=-0.89, p-value=1.5 10^{-3}) and height per dose (r^2=-0.96, p-value=5.8 10^{-5}) significantly affected the apparent volume of distribution of TA. It was also found that height influenced the elimination clearance (r^2=-0.80, p-value=8.9 10^{-3}). No other covariates significantly influenced the PK parameters of TA with a risk of 5% bilateral. The significant covariates were included one by one in the base model.

According to the results (Table 2), the model with the lowest BICc was the one for which IWD was added as a covariate for the volume of distribution. This model was considered as the final covariate model (model B).

The fixed effect parameters identified for the model B are summarized in Table 3.

The precision of the estimations obtained from the bootstrap mostly reached the required standards (≤30% for fixed parameters and ≤50% for $\boldsymbol{\omega}_P$) except for Q (RSE$\boldsymbol{\omega}_Q$ = 88 %) and V1 (RSE$\boldsymbol{\omega}_{V1}$ =69.7%). Diagnostic plots of the final model are presented in Fig. 3.

The proportion of outlier plasma and urinary concentration data individually predicted by the final covariate model were assessed respectively at 3.57% and 0%. Curves representing empirical percentiles were within the prediction intervals. NPDE plots were well distributed around the zero. The Shapiro Wilk test showed that their distribution was not significantly different from 0 (Fc = 0.973, p-value=0.26, for blood concentrations; Fc=0.870, p-value=0.12 for the urinary concentrations). The normal distribution of the η values was not rejected by any statistics at the 95% confidence level (Fc > 0.90, p>0.41).

When studying the time-course evolution of TA plasmatic concentrations in our study patients (Fig. 4), we observe a non-linear relation between the dose given and the C_{max} observed. In concordance with those observed concentrations, the results of the simulations performed also showed that the initial blood concentrations were higher when the dose given was 0.5 g than 1 g (Table 4). This revealed a non-linear relation between the C_{max} and the dose administered according to the simulated values (Table 4).

According to our model, the maximal blood concentration will be estimated with the following equation:

$$C_{max} = \frac{Dose}{V1_{pop} \cdot e^{\beta \cdot \frac{IW}{Dose}}}$$

This equation illustrates the non-linear relation between Cmax and the dose given. This non-linearity is explained by the positive asymptotic evolution of the volume of distribution of TA with the dose given.

Fig. 5 represents the observed concentrations of TA on the time with curves stratified according to the volume of additional blood loss. According to the correlation tests, results revealed the absence of correlation between the dose received and the additional blood volume (Vs2; r^2=0.009), a negative non-significant correlation between the predicted C_{max} and the Vs2 (r^2=-0.153, p-value=0.695), a positive non-significant correlation between the predicted AUC and the Vs2 (r^2=0.509, p-value=0.162).

4. Discussion

Our results support that TA kinetics are best described with a two-compartment model with a double linear elimination from the central compartment. The analyses showed that the ideal weight per dose (IWD) was the covariate which best explained interindividual variability when it was tied up to the volume of distribution.

This was the first study which estimated PK parameters of TA when used for the treatment of PPH.

The results supported by our study are consistent with the previous findings. Most studies described the two-compartment model with first-order elimination as being the most adequate PK model for i.v TA (Benoni et al., 1995; Dowd et al., 2002; Eriksson et al., 1974; Gertler et al., 2017; Grassin-Delyle et al., 2019; Grassin-Delyle et al., 2018; S. Grassin-Delyle et al., 2013; Stanislas Grassin-Delyle et al., 2013; Sharma et al., 2012; Wesley et al., 2015). A study proposed a three-compartment model with a third exponential curve starting 8 h after treatment (Pilbrant et al., 1981). As plasma samples weren't collected beyond 6 hours after treatment for our study, our results remain consistent with this last study.

In comparison with these latter studies, TA clearance appears increased in our study (10.6L/h versus 2.5-7.4L/h) and the volume of distribution appears smaller (12.3L versus 16.5 to 46.3L), while it is general knowledge that this latter parameter are in most cases increased in pregnant women. (Eriksson et al., 1974; Grassin-Delyle et al., 2019; Grassin-Delyle et al., 2018). The decrease in volume of distribution may be linked to the important loss of blood encountered during haemorrhagic caesarean section. Otherwise, if the assumption of consumption of TA turns out to be correct, the decrease in volume of distribution could be the consequence of the consumption of TA: the consumption of TA would cause the diminution of the free-TA concentration in the blood and therefore the decrease in the volume of distribution.

Two previous studies had completed their plasmatic dosages with urinary dosages in healthy volunteers in the past. These results supported that urinary excretion of TA was total in healthy volunteers (Eriksson et al., 1974; Pilbrant et al., 1981). However, our results pointed out that a double first-order elimination was the most appropriate to describe TA kinetics when adjusted on the quantity of TA excreted in the urine. The hypothesis of a non-urinary excretion in PPH could be easily explained by the excretion of TA in the haemorrhagic blood flow. To date, no PK study including urinary dosages were conducted in trauma, cardiac surgery or PPH. However, there are gaps in the interpretation of our model. First, if the amount of TA not excreted in the urines, was excreted in the haemorrhagic blood flow, this would represent an important quantity of TA. Yet, small additional volumes were measured for some patients (342 +/- 313 mL). Besides, our results showed a negative correlation (non-significant) between C_{max} and the Vs2, and a positive correlation between AUC and the Vs2 which leaded us to consider the consumption of tranexamic acid as a hypothetical mechanism of elimination. This assumption would also explain the increase in clearance, that may be bound to important TA consumption. In fact, if we calculate the renal clearance of TA in our tiny sample, we obtain a value of 2.76 which is low but coherent with the one observed in som trauma patients.(Grassin-Delyle et al., 2018). The half-time elimination estimated here is consistent with the one observed in previous studies (Eriksson et al., 1974; Grassin-Delyle et al., 2019; Grassin-Delyle et al., 2018). Special attention will have to be paid to the volume of distribution and the urinary clearance in the currently recruiting study.

The major mechanism of tranexamic acid relies on its binding to the t-PA-activated-plasminogen which blocks native fibrin lysin sites connection. We could assume that, following its binding on t-PA-activated-plasminogen,

TA could remain trapped on it. The method of dosage permit to determine the total amount of TA in urinary and blood samples but may be not able to detect trapped TA. Interestingly, trapped TA could be related to fibrinolysis intensity which is highly variable from one patient to the other. Dosages in haemorrhagic blood were planned to be performed in the TRACES survey to confirm either assumptions.

The multivariate regression analysis revealed a good correlation between the ratio IW/D and the apparent volume of distribution of TA. The main covariate that stood out from previous studies was BW (Dowd et al., 2002; Gertler et al., 2017; Grassin-Delyle et al., 2019; Grassin-Delyle et al., 2018; S. Grassin-Delyle et al., 2013; Stanislas Grassin-Delyle et al., 2013; Wesley et al., 2015). Our results didn't point out any correlation between BW and the volume of distribution of TA. However, they suggested a strong correlation between the volume of distribution and the dose and especially the variable IWD. With IWD as a covariate for the volume of distribution, the model had a 15.07-point lower corrected BIC value compared to the model with no covariate. As the strength of the evidence against the model with the higher BIC is very strong when the difference between to BIC values overtake 10 points, our results support that this covariate model provides a more precise estimation of TA kinetics than the base model. It sounded difficult to compare our estimated populational PK parameters obtained in context of immediate post-partum to other results as the previous PK studies were led in trauma(Grassin-Delyle et al., 2018) or in infant[21,23], children[21,22,23], neonates[21,23], adults[24-26] in cardiac surgery with cardiopulmonary bypass or in healthy volunteers (Benoni et al., 1995; Grassin-Delyle et al., 2019). As far as we know, the amount of TA administered hasn't been used as covariate for covariate testing in those studies. It seems plausible that the IW is better correlated with the volume of distribution than the BW is because of the influence of pregnancy on the BW. The fact that the volume of blood loss before inclusion (Vs1) was not significantly correlated with the volume of distribution of TA may due to the compensation of the loss by vascular filling.

The major limitation of our study is mainly tied up to the lack of data. The number of subjects included corresponds to what was planned in the published TRACES non-interventional pilot study protocol, with two patients excluded *a posteriori* for missing data or disrespect of sampling times. No control PK study was planned in the protocol as the administration of tranexamic acid is not recommended in non-hemorrhagic pregnant women. The dose of 0.5, 1g or 2g was left to the practitioners' appreciation. Yet, that number is consistent since this is a pilot study. Our results revealed a wide inter variability in initial plasma concentration data adjusted on the dose (RSE=69%) which is not explained by our model. Data provided by the TRACES study will be used to complete our model and investigate this variability.

Our model doesn't confer guidance for dose adjustment of TA as the targeted blood concentration remains uncertain. However, guidance in optimizing dose regimen is needed as far as TA used at high doses may lead to adverse effects (Couture et al., 2017; Hodgson et al., 2015). Several minimally effective blood concentrations of TA have yet been proposed in the literature, depending on the mechanism of action considered. It was found that 10 µg/mL of TA inhibited 80% of fibrinolysis when contacted with porcine tissues (Andersson et al., 1968). Otherwise, platelet-rich plasma incubated with 16 µg/mL of TA leads to a reduction by 50% plasmin-induced platelet activation, a study showed (Cortet et al., 2012). Finally, intrinsic generation of thrombin through activation of factor XII seemed to require concentrations of TA ranging from 126 to 252 µg/ml (Stief, 2009).

20 µg/mL of TA are basically assumed to be sufficient to inhibit the major part of fibrinolysis and this threshold has been already used to optimize TA dose regimen in clinical practise (Grassin-Delyle et al., 2018). The previous studies dealing with that topic were led in vitro. The relationship between blood TA concentration and blood loss has never been demonstrated. A recent article even showed that the TA concentrations maintained above 10 $mg.L^{-1}$ weren't correlated with blood loss reduction (Lanoiselée et al., 2018). The 20µg/mL threshold was reached for each patient and so for each dose tested in our study. Also, according to Fig. 4.a and 4.b, what differs most between the 3 different doses given is not the Cmax reached but the half-time of elimination. In our tiny sample, we didn't observe any link between the time spent above the 20µg/mL and the end of the additional bleeding (Fig. 5). There is currently no data establishing the threshold of 20µg/mL as the efficient one to reduce additional blood loss and inhibit fibrinolysis all together. This is the aim and the great interest of TRACES trial, in the way to be analyzed. Considering the gap between the populational volume of distribution estimated in our study and the one observed in healthy volunteers or trauma patients, we proceeded to a recalculation of what could be the efficacy concentration threshold. If we assume a median volume of distribution around 30 L for an efficacy concentration of 20µg/mL, the threshold quantity for a volume of distribution of 12.3L would be 50 µg/mL. The 50µg/mL threshold was reached for each patient and so for each dose tested in our study. We did not observe any relation between the time spent above the 50µg/mL and the end of the additional bleeding (Fig. 5).

Furthermore, the relation between the clinical efficacy of TA and the AUC has never been established to date. Comparing the AUC to the Cmax as markers of efficacy of TA could be a first step for determining the best pharmacodynamic indicator of TA. As the correlation between the AUC and the Vs2 was shown to be higher than the one between Cmax and Vs2 according to our results, the question of AUC as marker of efficacy needs to be investigate in future studies.

Additional blood volume was the only efficacy parameter collected according to the TRACES non-interventional pilot study protocol. The higher correlation between AUC and Vs2 than between Cmax and Vs2 forces us towards the assumption that the efficacy of TA is time dependent.

5. Conclusion

In summary, the population pharmacokinetic model of TA in haemorrhagic caesarean section was successfully established in our tiny sample of patients. The results of this preliminary TRACES pharmacokinetic study suggested that elimination of TA is partially non urinary in contrast with healthy patients. This raised the question of the secondary elimination of TA that we assumed to be either an haemorraghic elimination or a TA antifibrinolytic trapping. On-going TRACES trial is expected to corroborate either assumptions.

Declarations sections

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Compliance with ethical standards

Ethics approval

TRACES trial obtained approval from the competent national authorities (ANSM 201500249926) and the Ethics Committee (CPP 15/50 020216) before beginning the study, in accordance with article L1121-4 of the Public Healthcare Code. This trial has been declared on the clinical trials registration on 13 of june 2016 under the number CT 02797119. Registration will be performed in accordance with decree dated November 14, 2006 about gathering data in the national register of individuals participating in biomedical research.

Consent for publication

Authors and sponsors have given their consent and defined the publication rules.

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Conflict of interest

The authors declare no competing interest.

Credit Author Statement

S.Gilliot contributed to formal analysis, methodology, software, writing, review and editing of the final version. AS Ducloy-Bouthors contributed to conceptualization, funding acquisition, investigation, project administration, validation of the data, writing and revising the final version of the present manuscript submitted for publication. Benjamin Hennart contributed to conceptualization, data curation, formal analysis, methodology, validation, and revision the final version of the present manuscript submitted for publication. F Longeville contributed to methodology, formal analysis and revision. M Jeanne and G Lebuffe contributed to formal analysis and validation. P Odou contributed to methodology, formal analysis, validation and revision of the final version of the present manuscript submitted for publication.

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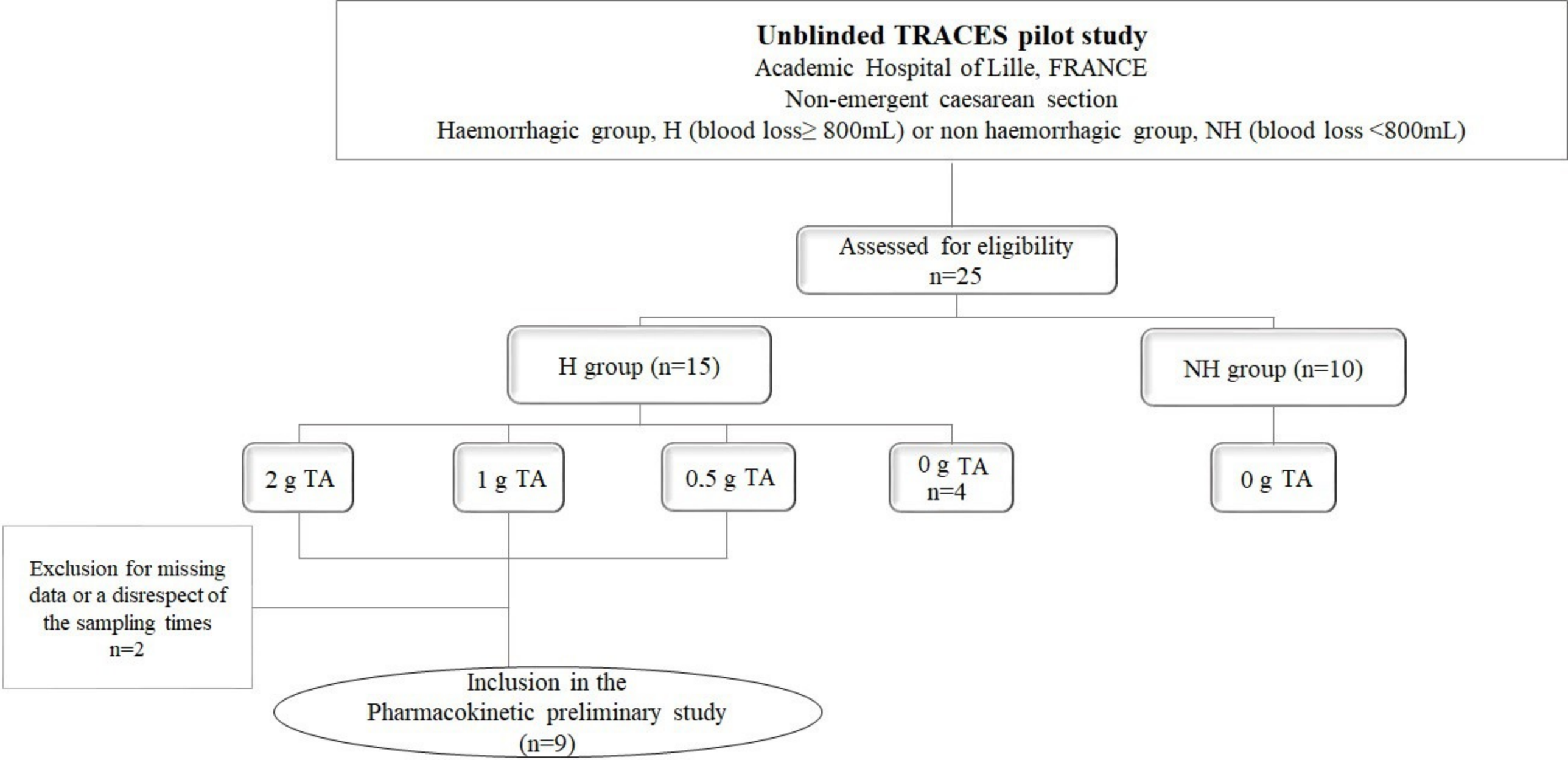
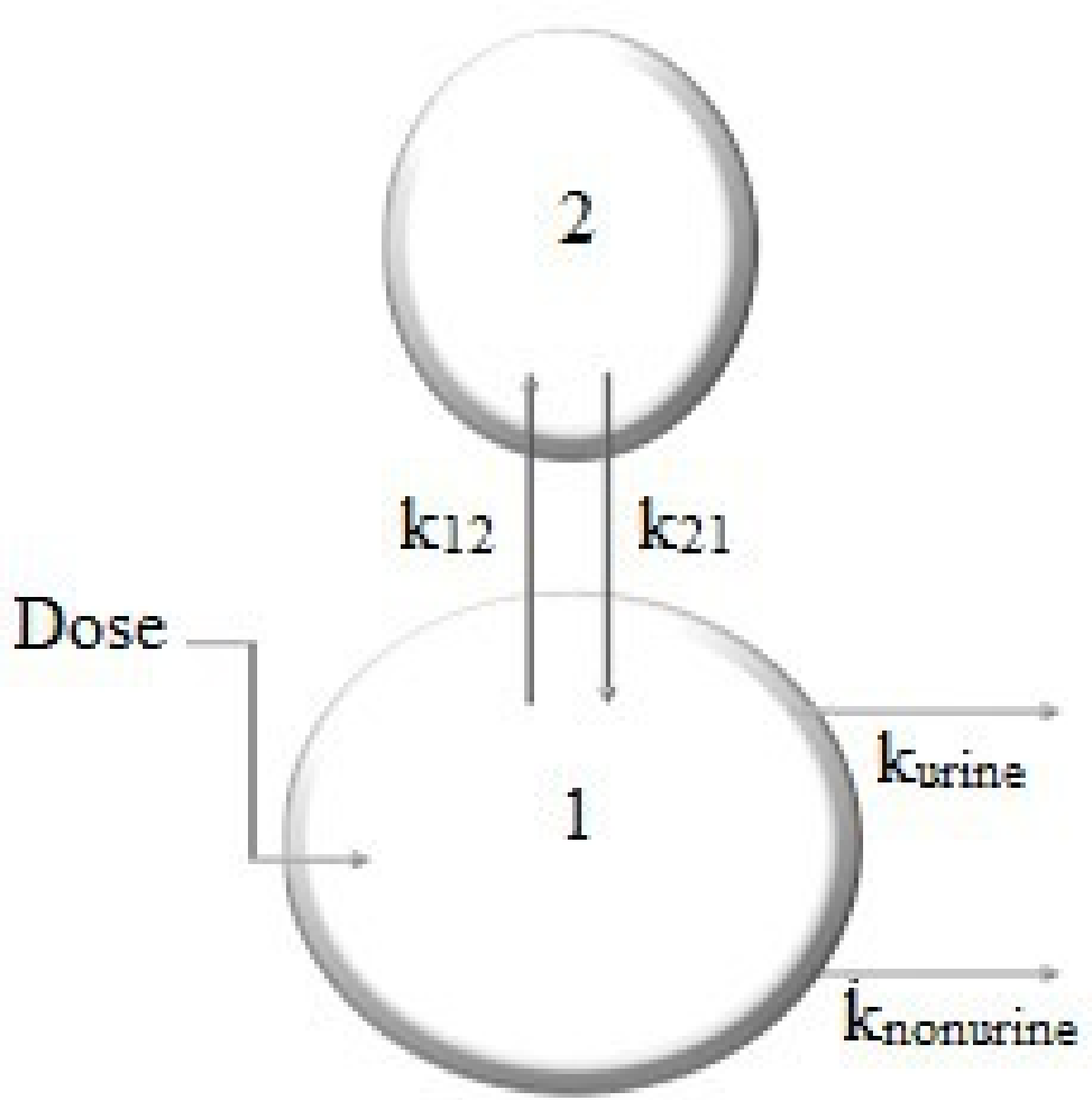

Unblinded TRACES pilot study
Academic Hospital of Lille, FRANCE
Non-emergent caesarean section
Haemorrhagic group, H (blood loss≥ 800mL) or non haemorrhagic group, NH (blood loss <800mL)
Assessed for eligibility
n=25
H group (n=15)
NH group (n=10)
2 g TA
1 g TA
0.5 g TA
0 g TA
n=4
0 g TA
Exclusion for missing data or a disrespect of the sampling times
n=2
Inclusion in the Pharmacokinetic preliminary study
(n=9)


2
k12
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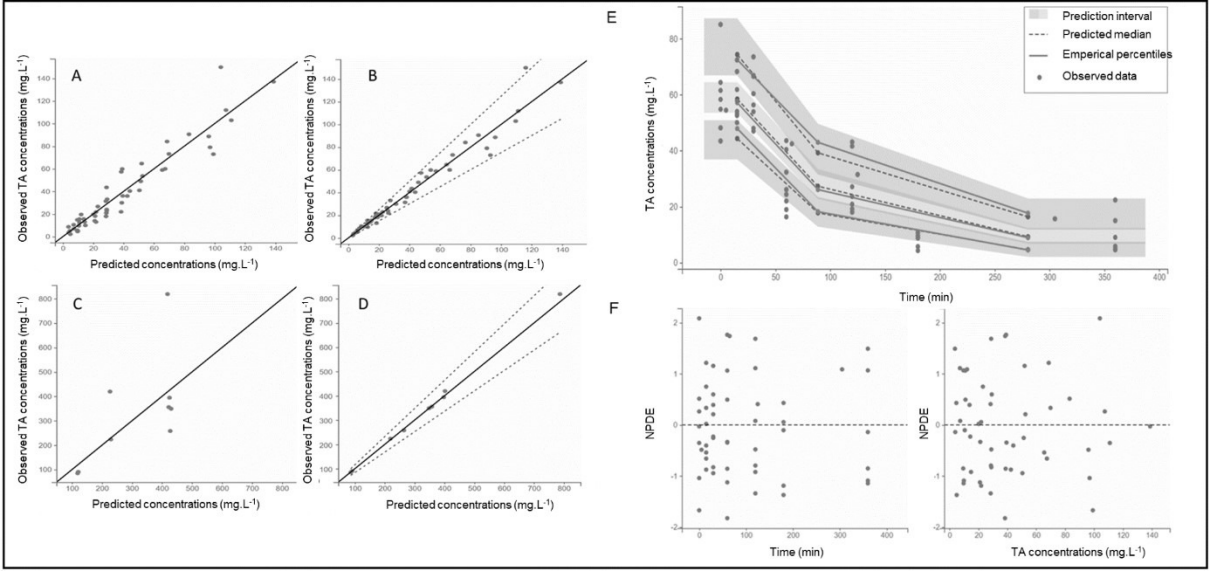
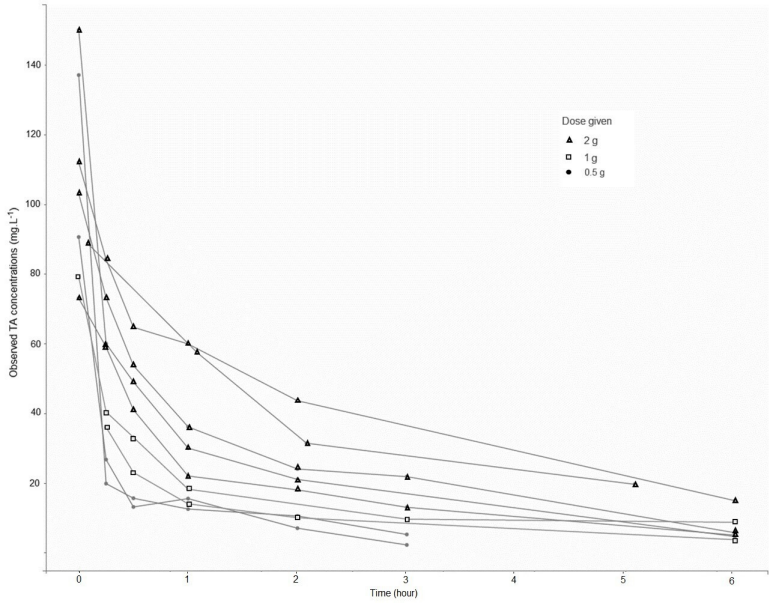
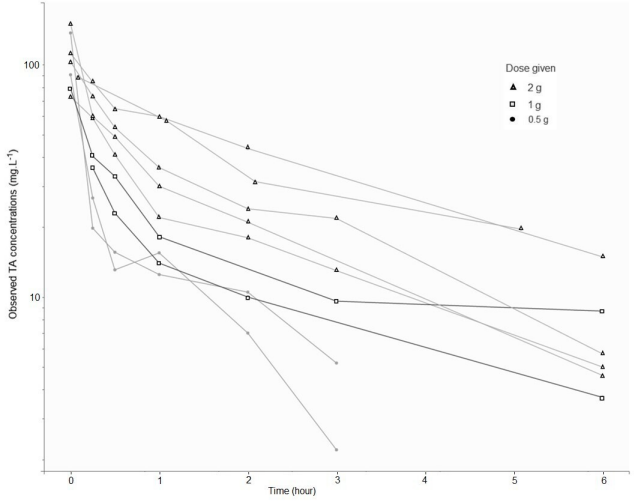
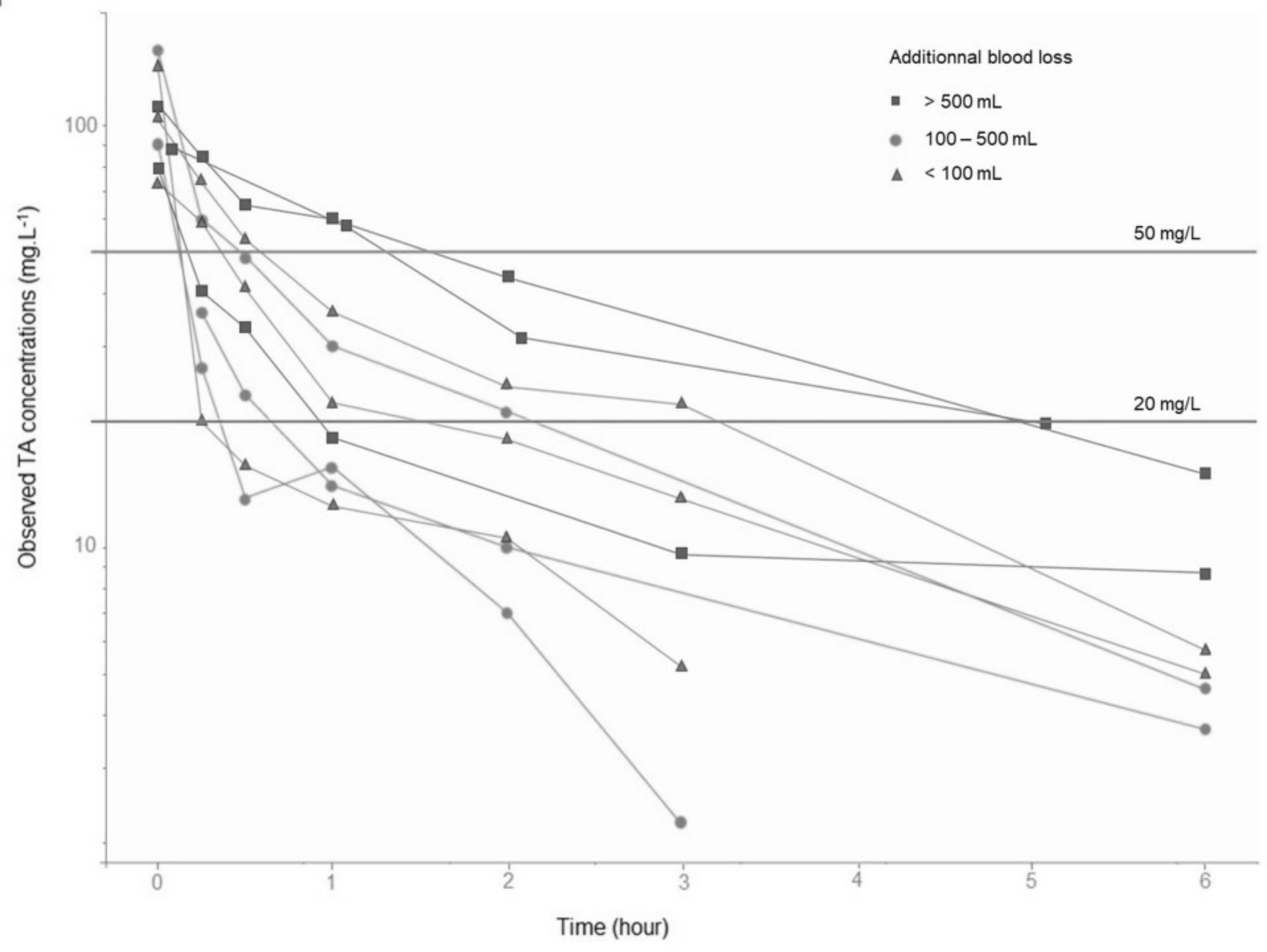

A
B
C
D
E
F
Observed TA concentrations (mg.L-1)
Predicted concentrations (mg.L-1)
Prediction interval
Predicted median
Emperical percentiles
Observed data
TA concentrations (mg.L-1)
Time (min)
NPDE
TA concentrations (mg.L-1)


Dose given
2 g
1 g
0.5 g
Observed TA concentrations (mg.L-1)
140
120
100
80
60
40
20
0
1
2
3
4
5
6
Time (hour)


Dose given
2 g
1 g
0.5 g
Observed TA concentrations (mg.L-1)
100
10
0
1
2
3
4
5
6
Time (hour)


Additionnal blood loss
> 500 mL
100 – 500 mL
< 100 mL
50 mg/L
20 mg/L
100
10
Observed TA concentrations (mg.L-1)
0
1
2
3
4
5
6
Time (hour)

Tables

Number of compartments	Elimination A	Elimination B	-2LL	BICc	Condition index
2	Non linear	.	515.04	554.92	12
2	Non linear	First-order	662.38	708.58	ND
2	Non linear	Non linear	626.31	685.15	ND
2	First-order	.	516.77	550.32	7.3
2	First-order	First-order	991.36	1031.24	ND
2	First-order	Non linear	678.86	725.06	ND
2	Double linear elimination	.	470.35	510.22	2.8
3	First-order	.	472.28	524.89	ND

Table 1. Selection criteria for the base model. Legend: BICc: corrected Bayesian Information Criterion, ND: undeterminable by the algorithm with 200 iterations.

Model	Parametrization	-2LL	BICc	κ
(A) Base model n°7	Cl, V1, V2, Q, p_{urine}	470.35	510.22	2.8
(B): (A)+ covariate effect	*$\log(V1) = \log(\theta_{V1}) + \beta \times IWD + \eta_{V1}$	449.50	491.57	21
	$\log(V1) = \log(\theta_{V1}) + \beta \times TD + \eta_{V1}$	450.20	492.27	23
	$\log(V1) = \log(\theta_{V1}) + \beta \times PFD + \eta_{V1}$	456.60	498.67	10
	$\log(V1) = \log(\theta_{V1}) + \beta \times D + \eta_{V1}$	457.15	499.23	110
	$\log(Cl) = \log(\theta_{Cl}) + \beta \times T + \eta_{V1}$	462.30	504.38	504
	$\log(Cl)=\log(\theta_{Cl}) + \log(T/160)^{\beta} + \eta_{Cl}$	462.35	504.42	3.1
(C): (B)* + covariate effect	$\log(Cl) = \log(\theta_{Cl}) + \beta \times IWD + \eta_{Cl}$	449.03	493.30	25
	$\log(V2) = \log(\theta_{V2}) + \beta \times IWD + \eta_{V2}$	449.23	493.50	79
	$\log(Q) = \log(\theta_{Q}) + \beta \times IWD + \eta_{Q}$	448.93	493.20	25
	$\log(p_{urine}) = \log(\theta_{purine}) + \beta \times IWD + \eta_{purine}$	449.12	493.39	31

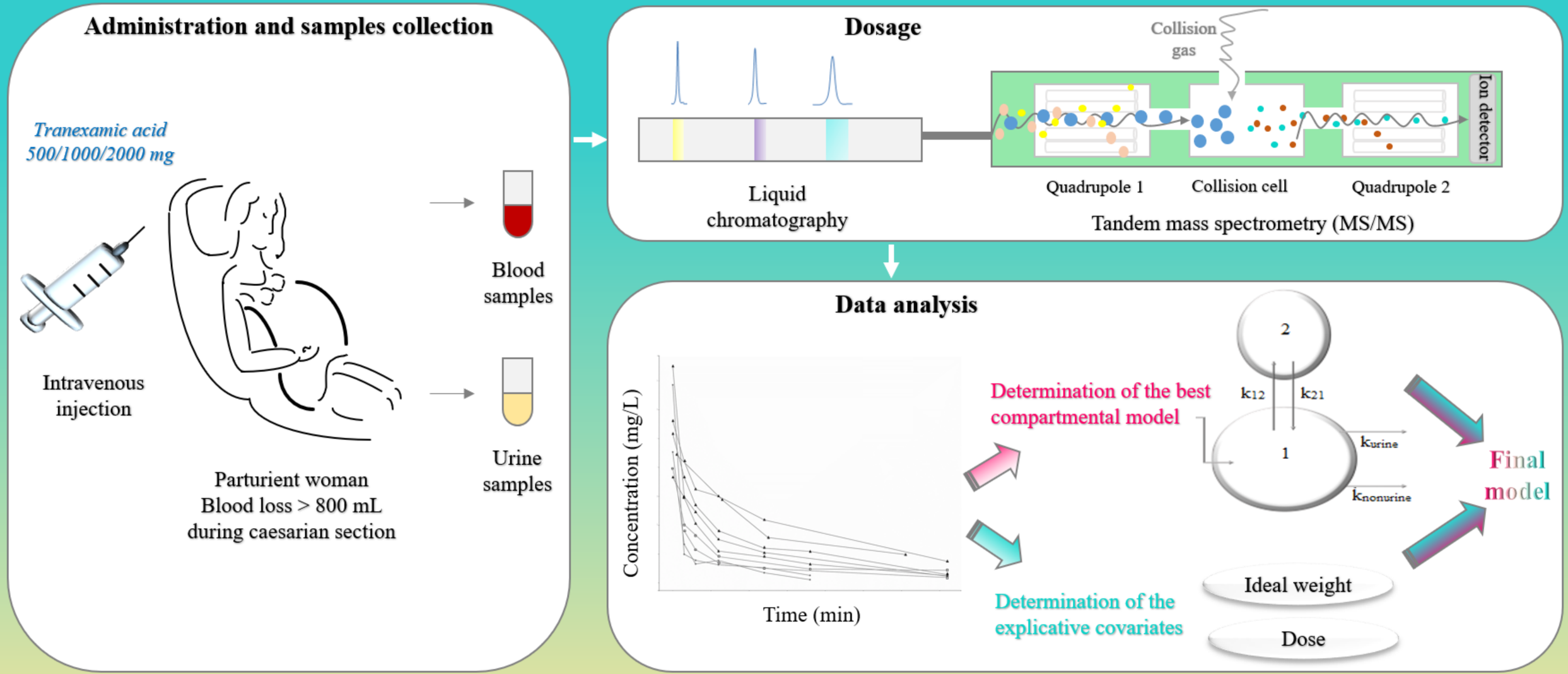
Table 2. Steps for pharmacokinetic model building. Legend : -2LL, maximized log-likelihood; BICc, corrected Bayesian information criterion; IWD, ideal weight per dose; HD, height per dose; BWD, bodyweight per dose; D, dose; H, height; κ, condition index, β, factor applicated to the covariate, η, between subject variability.

Parametrization		Original dataset		Bootstrap nboot=1000	
Population parameters	Covariate effect	Estimated values (RSE, %)	Shrinkage (conditional distribution) %	Median	RSE (%)
θ_{Cl} (L.min^{-1})	-	0.169 (11.0)	-2.76	0.171	11.1
θ_{V1} (L)	$e^{(\beta V1 \times IWD)}$	29.5 (12.1)	-9.98	29.4	16.1
β_{V1}	-	-17.6 (12.7)	NA	-17.3	23.7
θ_{Q} (L.min^{-1})	-	0.506 (11.0)	16.8	0.532	13.0
θ_{V2} (L)	-	15.8 (17.1)	-10.2	15.7	17.1
θp_{urine}	-	0.258 (13.9)	-5.62	0.358	16.2
ω_Cl (%)	-	31.9 (26.3)	-	29.4	20.6
ω_V1 (%)	-	8.89 (70.5)	-	6.4	69.7
ω_Q (%)	-	6.85 (151.0)	-	7.3	88.0
ω_V2 (%)	-	44.6 (32.0)	-	40.4	30.1
ω_p_urine (%)	-	40.0 (27.5)	-	35.0	28.3
b1	NA	0.151 (13.6)	NA	0.148	15.8

Table 3. Estimated population parameters for the final covariate model. The model was parameterized using elimination clearance (Cl), the volume of central (V1) and peripheral (V2) compartments, diffusional clearance (Q), urinary excretion fraction (p_{urine}). Legend : NA, non applicable; nboot= number of bootstrap samples performed, RSE, relative standard error; SD, standard deviation; b1, the fixed factor of the proportional residual error for the blood concentrations.

Estimated values	0.5 g	1 g	2 g	4 g
Patient's height of 1.5 m corresponding to an IW of 43.3 kg				
AUC ($mg.L.min^{-1}$) (median[Q1 ;Q3])	2,686 [2,314 ; 3,199]	5,015 [4,357 ; 5,901]	9,464 [8,218 ; 10,606]	18,640 [15,815 ; 20,908]
Cmax ($mg.L^{-1}$) (median[Q1 ;Q3])	76 [67 ; 85]	72 [66 ; 81]	101 [91 ; 115]	166 [150 ; 180]
Patient's height of 1.6 m corresponding to an IW of 52.4 kg				
AUC ($mg.L.min^{-1}$) (median[Q1 ;Q3])	2,786 [2,391 ; 3,316]	5,242 [4,465 ; 7,402]	9,852 [8,428 ; 11,484]	18,666 [15,991 ; 20,879]
Cmax ($mg.L^{-1}$) (median[Q1 ;Q3])	108 [94 ; 122]	86 [77 ; 96]	107 [94 ; 121]	171 [149 ; 190]
Patient's height of 1.7 m corresponding to an IW of 61.2 kg				
AUC ($mg.L.min^{-1}$) (median[q1 ;q3])	3,087 [2,650 ; 3,573]	5,396 [4,767 ; 6,389]	10,090 [8,656 ; 11,177]	18,920 [16,349 ; 21,385]
Cmax $(mg.L)^{-1}$ (median[Q1 ;Q3])	141 [126 ; 161]	98 [86 ;111]	117 [102 ; 132]	181 [163 ; 197]

Table 4. Maximal concentrations (Cmax) and area under the curve from 0 to 360 minutes (AUC) according to the simulation with individual randomization given by the final model for 1000 individuals receiving a single intravenous bolus doses of tranexamic acid (TA). Legend: IW, individual weight; Q1, first interquartile; Q3, third interquartile.


Administration and samples collection
Tranexamic acid
500/1000/2000 mg
Intravenous injection
Parturient woman
Blood loss > 800 mL
during caesarian section
Blood samples
Urine samples
Dosage
Liquid chromatography
Collision gas
Quadrupole 1
Collision cell
Quadrupole 2
Ion detector
Tandem mass spectrometry (MS/MS)
Data analysis
Concentration (mg/L)
Time (min)
Determination of the best compartmental model
Determination of the explicative covariates
2
1
k12
k21
kurine
knonurine
Final model
Ideal weight
Dose