Pharmacokinetics of tranexamic acid after intravenous, intramuscular, and oral routes: a prospective, randomised, crossover trial in healthy volunteers

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Abstract

Background: In response to the World Health Organization call for research on alternative routes for tranexamic acid (TXA) administration in women with postpartum haemorrhage, we examined the pharmacokinetics of TXA after i.v., i.m., or oral administration.

Methods: We conducted a randomised, open-label, crossover trial in 15 healthy volunteers who received i.v. TXA 1 g, i.m. TXA 1 g, or oral TXA solution 2 g. Blood samples were drawn up to 24 h after administration. Tranexamic acid concentration was measured with liquid chromatography–mass spectrometry, and the parameters of the pharmacokinetic models were estimated using population pharmacokinetics.

Results: The median time to reach a concentration of 10 mg L^{-1} was 3.5 min for the i.m. route and 66 min for the oral route, although with the oral route the target concentration was reached in only 11 patients. Median peak concentrations were 57.5, 34.4, and 12.8 mg L^{-1} for i.v., i.m., and oral routes, respectively. A two-compartment open model with body weight as the main covariate best fitted the data. For a 70 kg volunteer, the population estimates were 10.1 L h^{-1} for elimination clearance, 15.6 L h^{-1} for intercompartmental clearance, 7.7 L for the volume of central compartment, and 10.8 L for the volume of the peripheral compartment. Intramuscular and oral bioavailabilities were 1.0 and 0.47, respectively, showing that i.m. absorption is fast and complete. Adverse events were mild and transient, mainly local reactions and low-intensity pain.

Conclusions: The i.m. (but not oral) route appears to be an efficient alternative to i.v. tranexamic acid. Studies in pregnant women are needed to examine the impact of pregnancy on the pharmacokinetics.

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Keywords: administration routes; antifibrinolytic agents; pharmacokinetics; postpartum haemorrhage; tranexamic acid

Postpartum haemorrhage (PPH) affects 14 million women annually and is the leading cause of maternal death worldwide, responsible for over 50 000 deaths each year.[1] The World Maternal Antifibrinolytic (WOMAN) trial showed that early i.v. administration of tranexamic acid (TXA) reduces deaths from PPH.[2] When given within an hour of PPH onset, TXA reduces haemorrhage deaths by one-third.[3] Thereafter, the survival benefit falls by 10% for every 15 min delay until around 3 h after which there is no apparent benefit.[3]

In high-income countries, where most women give birth in hospital or have access to ambulance transport, doctors or paramedics can give i.v. TXA to those with PPH. However, in low- and middle-income countries, about 40% of women deliver at home, often with only rudimentary transport. Although health workers attend most births, many cannot give i.v. drugs. It can take several hours before a woman reaches a hospital, and some women exsanguinate before arrival. Although i.v. TXA is the treatment of choice for PPH, this route is not an option for tens of thousands of women.[4] The WHO recommends i.v. TXA as soon as possible but within 3 h of birth for all women with PPH and made 'the evaluation of benefits and potential harms of other routes of TXA administration' a research priority.[5]

Women with PPH can exsanguinate within minutes or hours. Tranexamic acid reduces bleeding by inhibiting fibrinolysis. The therapeutic challenge is therefore to achieve rapid inhibition of fibrinolysis in women with PPH. We previously showed that plasma TXA concentrations over 10 mg L^{-1} provide near-maximal inhibition of fibrinolysis, with concentrations over 5 mg L^{-1} providing some inhibition.[6] If these concentrations could be achieved after oral or i.m. TXA treatment, the use of these routes could expand access to this life-saving drug. Although the time to target concentration could be reduced by increasing the dose, women with life-threatening PPH are often too sick to swallow large volumes of liquid, and the i.m. dose is limited by the volume of TXA that can be given in a single i.m. injection (currently available TXA preparations are 100 mg ml^{-1}). To give the TXA 1 g dose that was shown to reduce PPH deaths in the WOMAN trial requires two 5 ml i.m. injections. Much larger volumes would be impractical. Only sparse pharmacokinetic data are available for i.m. TXA administration with no studies in women.[7–9] We examined the pharmacokinetics of i.v., i.m., and oral TXA treatments in healthy volunteers.

Methods

Study design

We conducted a randomised, open-label, crossover trial in healthy volunteers at the Clinical Investigation Centre of Necker Hospital, Paris, France. The study was approved by the London School of Hygiene & Tropical Medicine ethics committee (16286) and the Comité de Protection des Personnes Île de France III (2019-000285-38). Adult volunteers (non-pregnant women and men) aged between 18 and 45 yr, with a BMI ≥18 to ≤30 kg m^{-2} and body weight (BW) ≥50 to ≤100 kg, were invited to take part. Exclusion criteria were previous thrombotic event, abnormal coagulation tests, history of seizures, cardiovascular or renal disease, planned general anaesthesia or surgery in the 3 months after inclusion, pregnant or breastfeeding, visual disturbance, haematuria, allergy or other contraindications to TXA, use of any prescription or non-prescription medicine (including hormonal contraception) within 7 days before the first dose of the study drug is scheduled, inability to provide consent, and participation in trials within the past 1 yr where the total paid exceeded €4500.

Volunteers were recruited through advertisements in universities and on websites (Necker University Hospital, UFR Simone Veil–Santé [Montigny le Bretonneux, France] and Assistance Publique–Hôpitaux de Paris staff website). After eligibility was confirmed, a screening visit was scheduled when written informed consent was obtained. Consenting volunteers were randomly allocated into six treatment order groups (two to three patients per group) using a web-based randomisation system. The randomisation list was generated using Excel VBA macro by an independent statistician and was included in the electronic case report form so that participants received TXA by i.v., i.m., or oral route in six different orders. Although the order of routes should not influence the results, randomisation was done to standardise test conditions. Each volunteer received TXA by each of the three routes (i.v., i.m., and oral) on three separate days with a minimum washout period of 48 h between each treatment. For the i.v. route, TXA 1 g (10 ml of TXA 100 mg ml^{-1}) was given by slow infusion (approximately 1 ml min^{-1}). For the i.m. route, TXA 1 g (10 ml of TXA 100 mg ml^{-1}) was given as two 5 ml i.m. injections, administered in less than 30 s each. Each 5 ml was injected separately into the deltoid or vastus lateralis muscle using the Z-track method with the injection sites chosen according to the volunteer's preference and recorded. These sites were chosen, as they are most accessible for i.m. injection administration in the clinical emergency situation. For the oral route, TXA solution 2 g (20 ml of TXA 100 mg ml^{-1}) was swallowed. Volunteers attended three drug administration visits (V1, V3, and V5), each of which was followed by a 24 h post-drug administration visit (V2, V4, and V6).

Sample size and optimised sampling times for each administration route were determined using the PFIM 3.2.1 software (http://www.pfim.biostat.fr/)[10] to accurately estimate the pharmacokinetic parameters (relative standard errors <30%) based on data available in the same population.[7] Therefore, for the pharmacokinetic analyses, we took blood samples (0.5 ml venous blood in a dry tube without anticoagulant) immediately before TXA administration (T0), T0+5 min (i.v. route only), T0+30 min, T0+1 h, T0+2 h, T0+3 h, T0+4 h,

T0+5 h, T0+6 h, T0+8 h (i.m. and p.o. routes only), and T0+24 h. After each administration, we took one additional blood sample (0.5 ml venous blood in a sodium heparin tube) at one time point between T0+5 min and T0+8 h to investigate the distribution of TXA between red blood cells and plasma.

The primary endpoint was TXA concentration by time for each route. Secondary endpoints were pain score and duration of pain after TXA administration (VAS) at V1, V3, and V5; injection site reactions (redness, swelling, induration, tenderness, ecchymosis, necrosis, nerve injury, and infection) at visits V1–6; vital signs (BP, HR, and ventilatory frequency) at visits V1–6; known side-effects (fever, nausea, vomiting, diarrhoea, visual impairment, and seizure); and adverse events.

Sample analysis

We measured TXA concentrations in serum and whole blood samples using a validated liquid chromatography–mass spectrometry method. The lower limit of quantification is 0.1 mg L^{-1} and the linearity range 0.1–1000.0 mg L^{-1} with a precision <12.6% and an accuracy between 85.2% and 112.8%.[11]

Pharmacokinetic analysis

We analysed the data using the non-linear mixed-effect modelling program Monolix 2020R1 for compartmental population pharmacokinetics. We computed maximum likelihood estimators of the parameters without any approximation of the model (no linearisation) using a stochastic approximation expectation–maximisation algorithm combined with a Markov chain Monte Carlo procedure.[12] The number of iterations was fixed at 1000. The parameters of the two-compartment model were the first-order absorption constant for the i.m. (k_{aIM}) and oral (k_{aPO}) routes, i.m. (F_{IM}) and oral (F_{PO}) bioavailability, lag time before oral absorption (T_{lag}), elimination clearance (CL), intercompartmental clearance (Q), volume of central compartment (Vc), and volume of peripheral compartment (Vp).

The equations were as follows:

$$dA_1(t)/dt = INPUT - k_{10} \times A_1(t) - k_{12} \times A_1(t) + k_{21} \times A_2(t) \qquad (1)$$

$$dA_2(t)/dt = k_{12} \times A_1(t) - k_{21} \times A_2(t) \qquad (2)$$

where INPUT is, according to the administration route

$$INPUT_{ORAL.IM} = k_{as} \times A_S(t) \qquad (3)$$

Table 1 Characteristics of volunteers. Data are presented as median [25th–75th percentiles].

Parameter	Number of patients or median
Female/male, n	11/4
Age (yr)	25 [22–29]
Body weight (kg)	64.2 [56.0–71.8]
Height (cm)	170 [167–173]
BMI (kg m^{-2})	22.2 [20.1–24.6]
Ethnicity (Arab/Caucasian/other)	2/8/5
Site of i.m. injection, n	
Deltoid	9
Vastus lateralis	6

$$INPUT_{INFUSION} = RATE \qquad (4)$$

where A_S is the amount of drug at the site of absorption for the i.m. and oral routes (0 for the i.v. route), A_1 and A_2 are the amounts of drug in the compartments, k_{as} is the first-order absorption constant for each extravascular
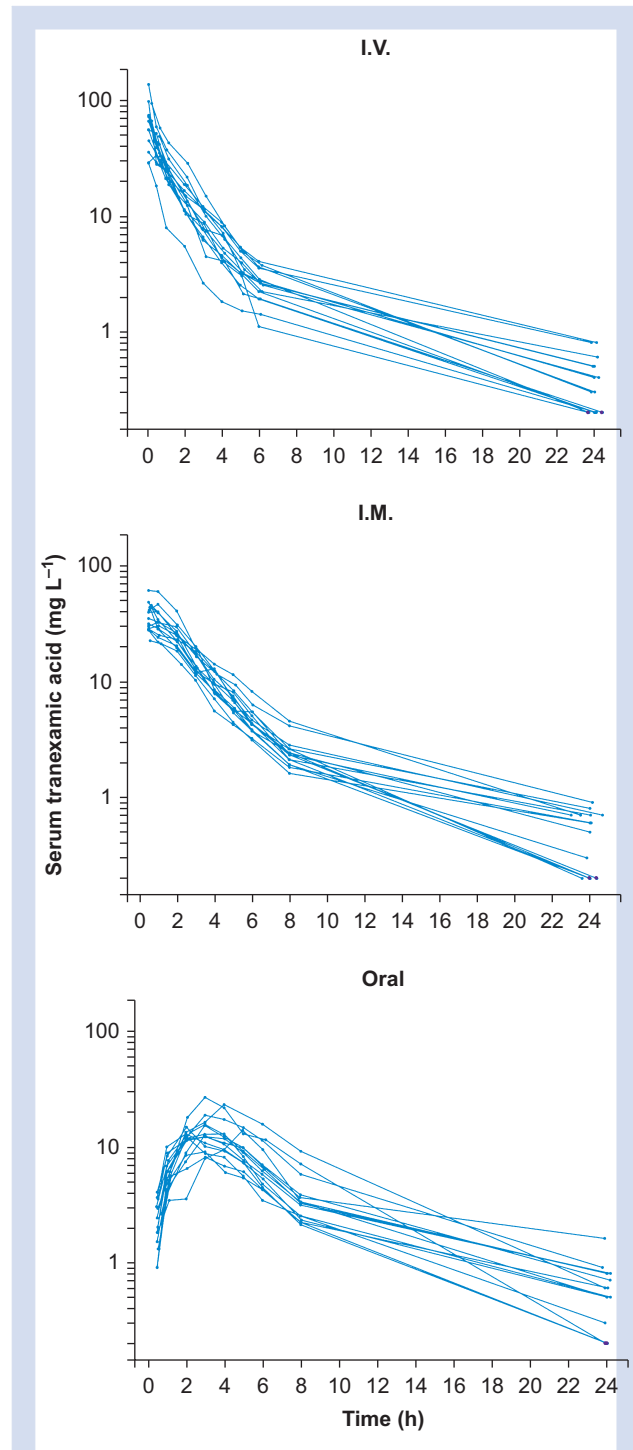

Fig 1. Observed serum tranexamic acid concentrations vs time for each administration route.

administration site (i.m. or oral), $k_{10}=CL/Vc$, $k_{12}=Q/Vc$, and $k_{21}=Q/Vp$.

Then, the drug concentration in the central compartment is

$$C=F_S \times A_1/Vc \qquad (5)$$

The relationship between serum and whole blood concentrations was described with the following equation:

$$C_{whole\ blood}=(1-Ht) \times C_{serum}+Ht \times C_{red\ cells} \qquad (6)$$

where Ht is the haematocrit. The red cell TXA concentration was estimated using the equation

$$C_{red\ cells}=\beta_{red\ cells} \times C_{serum} \qquad (7)$$

with $\beta_{red\ cells}$ a proportionality factor for the distribution of TXA from serum to red cells.

We investigated different error models (additive, proportional, or combined) to describe the residual variabilities (ε). We described between-subject variability (η) using an exponential model. We used the Bayesian information criterion (BIC) to examine the effect of including different model covariates, residual variability, and structure of the variance–covariance matrix for the ω parameters. We examined the effect of the following covariates: age, sex, BW, ethnicity, and site of i.m. injection. Parameter estimates were standardised for a mean standard covariate using a power function: $P_i=P_{STD} \times (COV_i/COV_{STD})^{PWR}$, where P_{STD} is the standard value of the parameter, and P_i and COV_i are the parameter and covariate values of the ith individual. The PWR exponents were estimated from the data. However, for BW, we used powers of 1 and 0.75 for volumes and clearances, respectively, consistent with allometric

scaling theory.[13] We evaluated the goodness of fit of each model by visual inspection of individual concentration–time courses, observed–predicted (population and individual) concentration plots, and prediction–corrected visual predictive checks. The Rsmlx R package (R Speaks Monolix; http://rsmlx. webpopix.org) was used to compute confidence intervals for the population parameters with non-parametric bootstrapping ($n=400$ bootstrap replicates) and log-likelihood profiling, and secondary pharmacokinetic parameters were calculated with Simulx 2020R1 (Lixoft).

Results

The 11 female and four male study participants had a median age of 25 yr and a median BW of 64.2 kg. Their characteristics are shown in Table 1. All participants had the three doses by each administration route, and there were no serious adverse events.

We collected 450 serum samples for TXA concentration measurement and 42 matched whole blood samples. The concentration *vs* time curves are shown in Figure 1. Two serum samples from the i.v. route, which had TXA concentrations greater than 430 mg L^{-1} at T0+5 min, were considered outliers and removed from the analysis. The model building steps are shown in Supplementary Table 1. A two-compartment open model with first-order absorption and elimination described the data better than a one-compartment model. A third compartment was not identifiable in our examination of three-compartment models. Log-normal distributions were used for all parameters, except oral and i.m. bioavailability for which a bounded [0, 1] logit-normal distribution was used. Adding a lag time for the oral absorption decreased BIC by 96 units. Adding site of injection

Table 2 Parameter estimates of the final population model. Parameters are normalised after a 70 kg subject body weight (BW) according to allometric scaling. BSV, between-subject variability (η); CI, confidence interval; NA, not applicable; % RSE, percent relative standard error. *F has a logit distribution; therefore, BSV for F is the BSV of the logit.

Parameter	Covariate effect	Bootstrap		Log-likelihood profiles	
		Estimate (90% CI)	BSV (90% CI)	Estimate (90% CI)	BSV (90% CI)
k_{aPO} (h^{-1})	—	0.28 (0.23–0.35)	0.36 (0.19–0.44)	0.28 (0.23–0.34)	0.35 (0.20–0.54)
T_{lag} (h)	—	0.43 (0.42–0.46)	NA	0.43 (0.41–0.46)	NA
F_{PO}	—	0.47 (0.35–0.62)	0.89* (0.43–1.32)	0.47 (0.36–0.57)	0.91* (0.59–1.33)
k_{aIM} (h^{-1})	—	1.25 (1.05–1.55)	NA	1.26 (1.11–1.44)	NA
F_{IM}	—	1.0 (1.0–1.0)	NA	1.0 (NA–NA)	NA
CL (L h^{-1} [70 kg]$^{-1}$)	$(BW/70)^{0.75}$	10.1 (9.4–11.1)	0.17 (0.10–0.22)	10.2 (9.3–11.2)	0.17 (0.16–0.22)
Q (L h^{-1} [70 kg]$^{-1}$)	$(BW/70)^{0.75}$	15.6 (11.1–25.2)	NA	15.7 (11.7–20.6)	NA
Vc (L [70 kg]$^{-1}$)	$(BW/70)^1$	7.7 (5.5–9.6)	0.44 (0.26–0.67)	7.6 (6.1–9.9)	0.44 (0.32–0.58)
Vp (L [70 kg]$^{-1}$)	$(BW/70)^1$	10.8 (9.6–12.3)	NA	10.8 (9.7–11.9)	NA
$\beta_{red\ cells}$	—	0 (fixed)	NA	0 (fixed)	NA
Correlation BSV$_{CL}$ *vs* BSV$_{Vc}$	—	0.842 (0.640–0.999)	NA	0.851 (NA–NA)	NA
Residual variability, serum concentration, proportional	NA	0.18 (0.13–0.22)	NA	0.18 (0.16–0.20)	NA
Residual variability, serum concentration, constant (mg L^{-1})	NA	0.53 (0.44–0.66)	NA	0.53 (0.44–0.64)	NA
Residual variability, whole blood concentration, proportional	NA	0.29 (0.24–0.33)	NA	0.29 (0.24–0.36)	NA

(vastus lateralis or deltoid) as a covariate for the absorption parameters of the i.m. route did not improve the model. Adding the effect of allometrically scaled BW on CL, Q, Vc, and Vp further decreased BIC by 19 units and $\sum \eta^2$ from 1.17 to 1.04. Age, sex, and ethnicity had no apparent effect on the pharmacokinetics. During the model building procedure, the $\beta_{red\ cells}$ estimate was not significantly different from 0, and this parameter was fixed at 0. The distribution of TXA into red cells appears negligible, and the serum TXA concentration can be calculated from the whole blood concentration using the formula $C_{serum} = C_{whole\ blood} \times 1/(1-Ht)$. Table 2 shows the population pharmacokinetic estimates, with confidence intervals calculated with both non-parametric bootstrapping and log-likelihood profiling. Log-likelihood profiles of the parameters are shown in Supplementary Figure 1, and Supplementary Figure 2 shows the individual TXA serum concentration–time profiles. For a 70 kg patient, the population estimates were 1.25 h^{-1} for the i.m. absorption constant (i.e. a 33 min absorption half-life), 1.0 for i.m. bioavailability, 0.28 h^{-1} for the oral absorption constant (i.e. a 2.5 h absorption half-life) with a lag time of 0.43 h, 0.47 for oral bioavailability, 10.1 L h^{-1} for elimination clearance, 15.6 L h^{-1} for inter-compartmental clearance, 7.7 L for the volume of the central compartment, and 10.8 L for the volume of the peripheral compartment.

The residual variability was estimated using a combined error model for the serum concentrations and a proportional error model for whole blood concentrations. Between-subject variabilities were estimated for k_{aPO}, F_{PO}, CL, and Vc using an exponential model. Figure 2 shows the predicted vs observed serum concentrations, and Figure 3 shows the prediction–corrected visual predictive check plot for the final population pharmacokinetic model. Supplementary Figure 3 shows observed-to-predicted TXA concentrations vs time plots. Individual TXA concentration–time profiles and diagnostic plots for whole blood concentrations and further diagnostic plots (residuals and normalised prediction distribution error plots and convergence diagnosis) are shown in Supplementary Figures 4–8.

Maximum plasma concentration (C_{max}), time to C_{max} (T_{max}), time to reach the target therapeutic concentration of 10 mg L^{-1}, and duration above this target were also calculated from the pharmacokinetic model. As shown in Supplementary Table 2, the median time to reach a therapeutic concentration of 10 mg L^{-1} was 4 min for the i.m. route and 66 min for the oral route, although with the oral route the target concentration was reached in only 11 patients. For the i.v. route, it can be considered that the maximal concentration, which is much greater than 10 mg L^{-1} for a 1 g dose, is reached at the end of the infusion. Once reached, the concentration remained above target for 2.9 h with i.v. TXA, 3.4 h with i.m. TXA, and 2.7 h with oral.

All adverse events are shown in Supplementary Table 3. Fifteen events were observed, amongst which two were likely
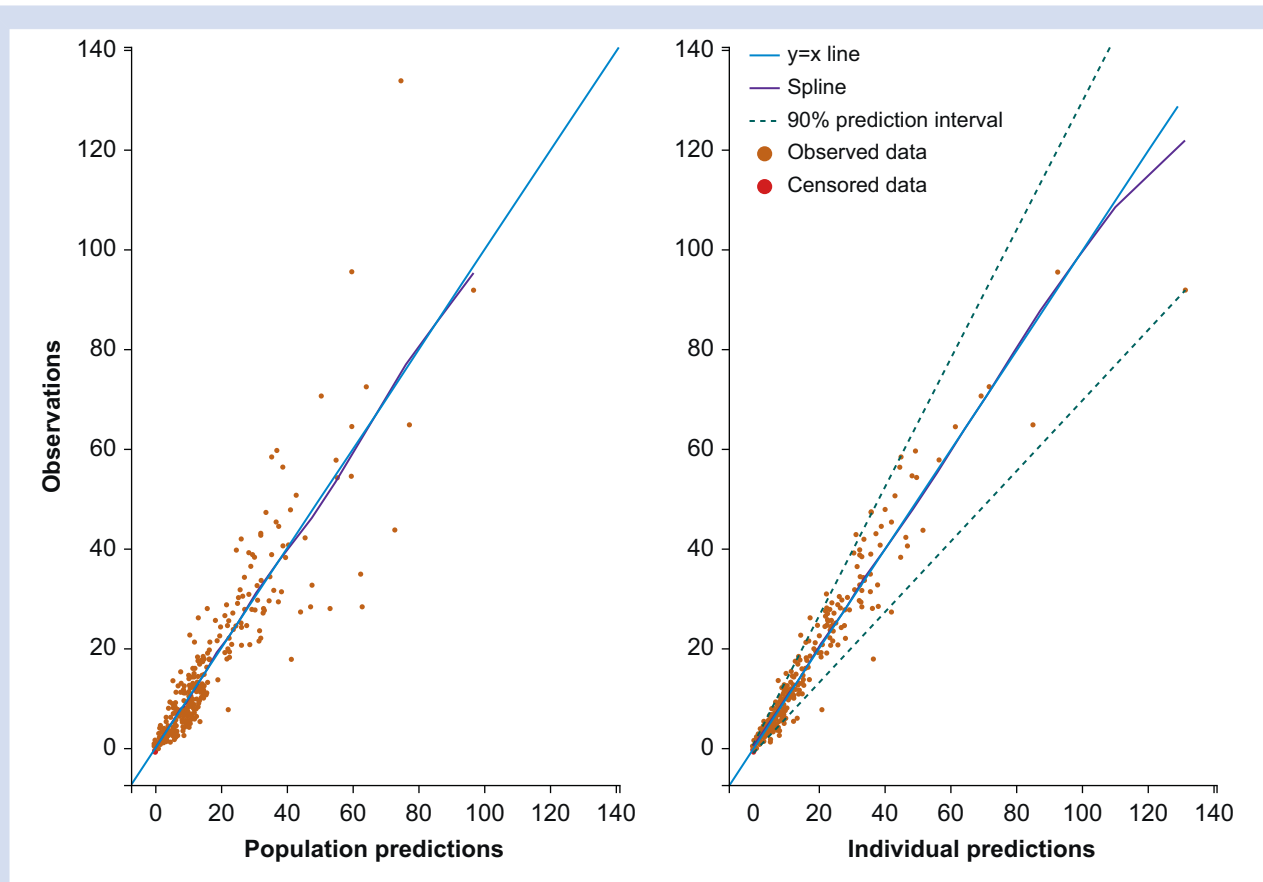

Fig 2. Observed serum tranexamic acid concentrations vs population and individual predictions. Red dots are values below the lower limit of quantification.
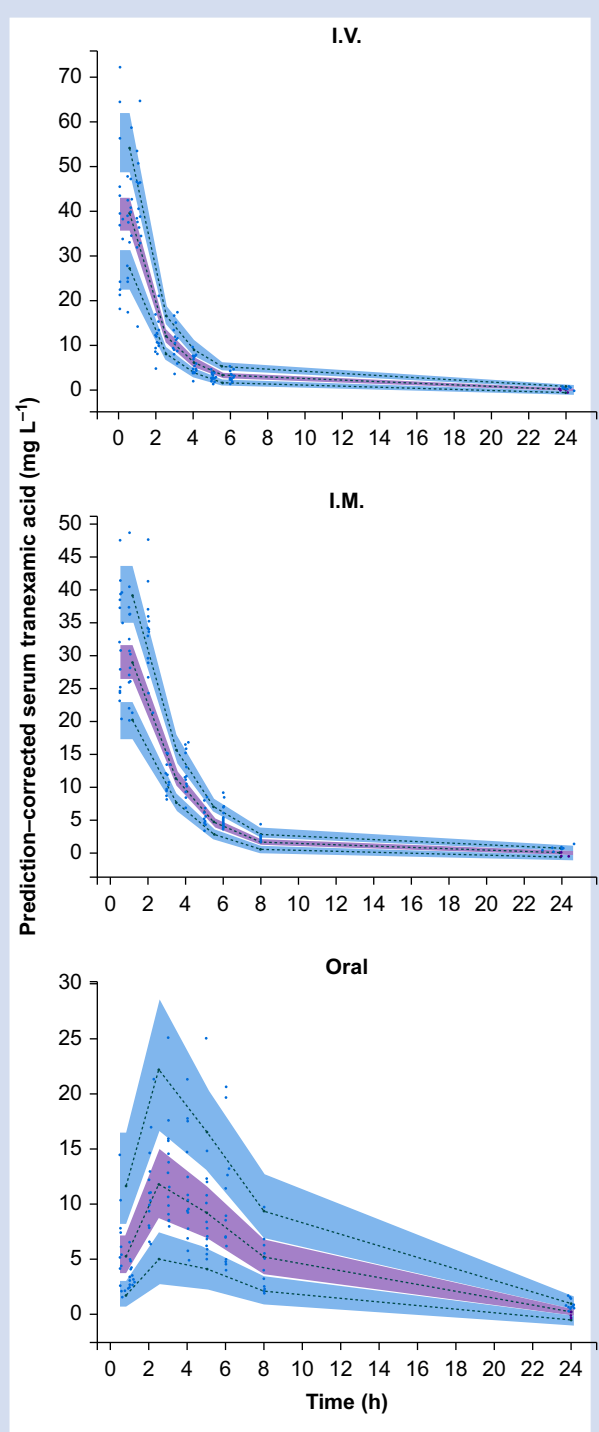
Fig 3. Diagnostic plots for the final population pharmacokinetic model: prediction–corrected visual predictive check for tranexamic acid serum concentrations. Blue dots depict measured tranexamic acid concentrations. The solid centre lines stand for the 5th, 50th, and 95th percentiles of observations and the shaded areas for the 95% confidence interval of the corresponding predictions. Red dots are values below the lower limit of quantification.

related to treatment. These were local reactions after i.v. administration: two patients had redness and one patient experienced pain during canula insertion. Pain was also recorded after each administration: four patients had pain after i.v. administration (median VAS score=1.5; duration <2 h except for one patient who had a residual pain [VAS score=1] for 6 h), 13 patients had pain after i.m. administration (median VAS score=2; duration <2 h), and two patients reported pain after oral administration (VAS score=2 for both; duration <2 h).

Discussion

In response to the WHO call for research on alternative routes for TXA administration, we conducted a randomised, crossover trial in healthy volunteers to examine the pharmacokinetics of TXA after i.v., i.m., and oral administration. We found that i.m. TXA is rapidly and completely absorbed, achieving the target (10 mg L^{-1}) therapeutic concentration within 5 min and remaining above this level for approximately 3.5 h. These results are in line with the results from our recent study using physiologically based pharmacokinetic modelling.[9] In contrast, oral TXA solution is absorbed slowly and incompletely, reaching the target concentration in only 11 of the 15 participants at about 66 min, with a bioavailability of 47%. All routes were well tolerated with only mild local reactions at the i.v. injection site in two patients. Pain was more common with the i.m. route, but its intensity was low and its duration was short.

Before this study, there were little data on the pharmacokinetics of i.m. TXA, and almost all of the data were from men. Most of our participants were women, and the crossover design allowed accurate estimation of bioavailability, minimising inter-individual variability. We found that sex, age, and ethnicity had no effect on pharmacokinetic parameters. Similarly, for the i.m. route, the site of injection (vastus lateralis or deltoid) had no apparent effect. Our estimates of the pharmacokinetic parameters are broadly in agreement with previous studies. An individual participant data meta-analysis of pharmacokinetic studies in healthy volunteers found that the population estimates were 7.6 L h^{-1} for clearance, 17.9 L for the volume of the central compartment, 2.5 L h^{-1} for the diffusional clearance, and 16.6 L for the peripheral volume of distribution for a 70 kg participant; oral and i.m. bioavailabilities were 46% and 105%, respectively, and the main covariate was allometrically scaled BW.[7] The elimination clearance in adults from previous studies was in the range 4.8–7.9 L h^{-1} for patients undergoing surgery or patients who have a history of trauma,[8,14–19] which is consistent with the clearance documented here for healthy volunteers. A recently reported pharmacokinetics study in 30 women undergoing Caesarean delivery who received i.v. TXA estimated a clearance of 9.4 L h^{-1},[20] but there were no data on oral or i.m. absorption in this patient population.

The main limitations are related to the study population, as young and healthy volunteers were included. We therefore did not investigate the effect of age or BW through a wide range, or the effect of renal impairment and other clinical conditions. Also, the i.m. administration consisted of two 5 ml injections. This may cause discomfort in volunteers, and absorption may be different from that observed with a single 10 ml injection. However, the latter volume is not compatible with i.m. injection, and 100% bioavailability was observed. Finally, this study

may be underpowered to detect an influence of some covariates, such as ethnicity or injection site, for the i.m. route.

Taken together, our data suggest that the i.m. route may be a safe alternative to i.v. TXA in women with PPH and in bleeding patients who have a history of trauma, provided that the necessary studies are conducted to demonstrate its efficacy. Considering that the marketing authorisation for TXA recommends a slow i.v. infusion over 10 min, the i.m. route achieves clinically effective levels within about 5 min and does not require i.v. cannulation. The i.m. absorption phase avoids the high peak concentration seen with i.v. administration, potentially avoiding dose-dependent adverse effects but maintains an effective concentration for a longer period than with i.v., potentially avoiding the need for repeat TXA dosing. Further studies of i.m. TXA in pregnant women are needed to examine the impact of the increased volume of distribution and increased renal elimination that are seen in pregnancy. Other studies needed include comparing the efficacy and safety of i.m. and i.v. TXA in women who are bleeding or at risk of bleeding after childbirth.

Authors' contributions

Study design: SG-D, J-MT, IRo, HS-S
Drafting of protocol: SG-D, IRo, HS-S
Supervising of drug assays: SG-D
Developing of analytical methods: EL
Carrying out of assays: EL, IRu
Formulating of pharmacokinetic methodology: FF, NB
Performing of pharmacokinetic analysis: SG-D, SU
Handling of trial administration: MA
Drafting of paper: SG-D, IRo, HS-S
Critical revising of paper: J-MT
MS was principal investigator at the recruiting site. All authors were responsible for reviewing and revising the paper and have approved the final version. The corresponding author had full access to all the data and had final responsibility for the decision to submit for publication.

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Declarations of interest

The authors declare that they have no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bja.2021.10.054.

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