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Original Article

Evaluating Tranexamic Acid Dosing Strategies for Postpartum Hemorrhage: A Population Pharmacokinetic Approach in Pregnant Individuals

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Abstract

Tranexamic acid (TXA) is used for the treatment and occasionally prevention of postpartum hemorrhage (PPH); however, questions still remain regarding dosing regimen optimization. This study evaluated TXA pharmacokinetic (PK) data from four clinical trials (NCT: 04274335, 03287336, 00872469, and 02797119) conducted in pregnant participants receiving intravenous, intramuscular, or oral TXA to prevent or treat PPH. The goal of this analysis was to comprehensively characterize TXA PK in a large, heterogeneous population of pregnant individuals to (1) assess the need for weight-based dosing and (2) compare exposure target attainment for alternative routes of administration. A population PK analysis was performed using nonlinear mixed-effects modeling in Pumas, and a stepwise approach was implemented to select the structural model and identify significant covariates. A total of 211 pregnant participants who received between 0.35 and 4 g of TXA intravenously, orally, or intramuscularly offered 1303 TXA plasma concentrations for model development. A two-compartment model with first-order elimination and first-order absorption for both intramuscular and oral administration best described the disposition of TXA. Actual body weight was the only statistically significant covariate identified, but inclusion into the model did not explain a substantial amount of the observed variability. Simulations of virtual pregnant individuals indicated minimal differences in TXA exposure between fixed and weight-based dosing regimens, supporting the use of fixed dosing. Intramuscular TXA was additionally found to be a viable alternative to intravenous administration, achieving similar target exposure metrics.

Keywords

modeling, pharmacokinetics, postpartum hemorrhage, simulation, tranexamic acid

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Introduction

About 14 million individuals suffer from postpartum hemorrhage (PPH) worldwide every year after childbirth and about 70,000 individuals die from PPH morbidity.[1] Although the definition varies and it can be difficult to measure accurately, PPH is often diagnosed as blood loss greater than or equal to 1000 mL within 24 h of delivery.[2] Hemorrhage was the most common cause of direct maternal death worldwide (27.1%), with PPH responsible for 480,000 deaths (19.7%) between 2003 and 2009.[3,4] In the United States, PPH accounts for 11% of maternal deaths.[5]

In 2017, the results of the World Maternal Antifibrinolytic Trial, a large, randomized controlled trial, showed that early use of tranexamic acid (TXA) reduces death due to bleeding in individuals with PPH, regardless of cause.[6] TXA is a lysine derivative and a synthetic antifibrinolytic that competitively inhibits the activation of plasminogen.[7] The World Health Organization updated their treatment recommendations to include 1 g intravenous (IV) administration of TXA, repeated once after 30 min for ongoing bleeding, as a standard PPH treatment and life-saving intervention.[8] Current International Federation of Gynecology and Obstetrics (FIGO) guidelines likewise recommend TXA to be administered as a 1 g IV infusion over 10 min soon after PPH diagnosis and within 3 h of birth.[9] However, additional research into the optimal route and dose of TXA is needed for the prevention and treatment of PPH in pregnant individuals.

TXA has been administered via IV, intramuscular (IM), and oral routes, and has been well characterized in non-pregnant individuals. Of note, TXA is primarily renally excreted (95% unchanged) with a volume of distribution of 9-12 L, total body clearance of 110-116 mL/min, and elimination half-life of approximately 2 h.[7] The bioavailability of TXA has previously been estimated as 100% IV and 45% for the IM and oral routes, respectively.[10,11] However, differences in TXA PK are likely to be observed in pregnant individuals during caesarean delivery due to alterations of body mass, pregnancy-induced physiological changes, and surgery-induced changes that may impact both volume and clearance. To optimize the benefits and minimize the risks of TXA for the treatment and prevention of PPH, TXA PK needs to be adequately characterized in a large, heterogeneous pregnant population. The purpose of this research was to therefore develop a population PK model from pregnant individuals receiving TXA across different studies to (1) assess the need for weight-based dosing and (2) compare exposure target attainment for alternative routes of administration.

Methods

Study Selection Criteria and Design

This research was deemed to be non-human subjects research by both George Washington University and the University of Maryland, Baltimore IRB offices. Studies with published results were considered for model development if they met the following criteria: (1) The study population was adult pregnant or immediately postpartum individuals, (2) The intervention was administration of TXA by either IV, IM, or oral route at the time of delivery, and (3) Blood samples for TXA plasma concentration measurement were collected. A total of four studies were identified as viable with willing participation from corresponding authors. A comprehensive summary of each study can be found in Table SA1.

The first was a prospective, interventional, non-randomized, single-center study to evaluate the pharmacokinetics and pharmacodynamics of TXA administered after delivery in people at risk of PPH (NCT03863964).[12,13] Each participant received 1 g TXA administered as a 10-min IV infusion immediately after umbilical cord clamping. Blood samples for TXA plasma concentration measurement were then collected at 3-, 7-, 15-, and 30-min post-infusion and then every 30 min up to 5 h post-infusion. The second study was a multicenter, randomized, double-blind, placebo-control therapeutic and pharmaco-biological dose ranging study to measure the effect on blood loss reduction of a single IV infusion of two dose regimens of TXA administered at the onset of an active PPH during elective or non-emergent cesarean section (CS) (NCT02797119).[14] Participants were administered either 0.5 or 1 g TXA as a 1-min IV infusion, with a rescue second dose of 0.5 g or 1 g given if hemorrhage became severe. Blood samples for TXA plasma concentration measurement were then collected at 15-, 30-, 60-, 120-, 180-, and 360-min post-dose. The third study was an open-label, randomized, multicenter trial to assess the pharmacokinetics and pharmacodynamics of IM, IV, and oral solution administration of TXA in individuals giving birth by CS (NCT04274335).[15] Participants were randomized to receive either 1 g IV TXA over 10 min, 1 g TXA as two separate IM injections, 4 g TXA oral solution, or no TXA. Blood samples were then collected for TXA concentration measurement pre-dose and post-dose at 15 ± 5 min, 30 ± 15 min, $1\text{ h} \pm 30$ min, 2 ± 1 h, 4 ± 1 h, 8 ± 1 h, 12 ± 2 h, and 24 ± 2 h. The fourth study was a prospective, open-label, single-center dose finding PK study in individuals scheduled for non-emergent CS who are at risk of hemorrhage (NCT03287336).[16] Participants received either 5, 10, or 15 IV TXA administered over 15 min at the time of umbilical cord clamping, with a 1 g cap as the maximum

administered dose. Blood samples were then collected for PK analysis pre-dose, and 10 min, 30-60 min, 1.5-3 h, 4-6 h, 7-8 h, and 24 h post end-of-infusion.

Bioanalytical Methods

Study NCT03863964 measured TXA plasma concentration by ultraperformance liquid chromatography (UPLC) tandem mass spectrometry detection, with a lower limit of quantification (LLOQ) for TXA of 2 to 5 μg/mL.[12] In study NCT02797119, TXA plasma concentration was measured using a liquid chromatography system coupled with tandem mass spectrometry. This method had a LLOQ of 2 mg/L and a calibration range of 5 to 200 mg/L.[17] Study NCT04274335 measured TXA concentrations in whole blood using a validated liquid chromatography-mass spectrometry method. The LLOQ was 0.1 mg/L with a linear range of 0.1 to 1000 mg/L.[18] Conversion from whole blood TXA concentration to plasma TXA concentration was performed for this analysis using the previously published methodology.[19] Study NCT03287336 measured TXA plasma concentration by ultra-high performance liquid chromatography-tandem mass spectrometry, with an LLOQ of 0.04 μg/mL for TXA.[20]

Software and Estimation Methods

The analysis was performed using nonlinear mixed-effects modeling in Pumas (version 2.0, Pumas AI, Baltimore, MD, https://pumas.ai/). First-order conditional estimation (FOCE) was applied to fit the pooled PK data and estimate typical values of PK parameters, the between-subject variability (BSV) for typical PK parameters, as well as the within-subject variability. BSV was incorporated as exponential random error models on model parameters, assuming a log-normal distribution:

$$P_i = P_{pop} \times e^{\eta i}$$

P_i is the individual PK parameter estimate for participant i, P_{pop} is the typical population value for the PK parameter, and η_i is the individual random effect estimate representing the deviation from P_{pop} for participant i and assumed from a normal distribution with a mean of zero and variance ω^2. This assumption was tested by visual inspection of the empirical Bayes distribution. Correlations between random effects were likewise explored visually. For interpretation purposes, BSV was expressed as percent coefficient of variation (%CV), which was approximated to $100 \times \sqrt{\omega^2}$ for the exponential random error models with small ω^2 estimates (i.e., <30%) or calculated as $\sqrt{\exp(\omega^2) - 1} \cdot 100\%$ for larger ω^2 estimates (i.e., ≥30%). Additive, proportional, and combination residual error models were likewise compared to describe the variability in the difference between the individual predictions and observations that remained unexplained. Examples of such unexplained errors could be due to bioanalytical assay errors, dosing inaccuracies, or other human errors throughout the recording process.

Model Selection Criteria

Model selection was based on comparison of the objective function values (OFV) between nested models or Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) for non-nested models. A reduction in OFV of 3.84 for 1 degree of freedom was considered to be statistically significant. Model misspecification was assessed by visual inspection of the individual weighted residual (IWRES) versus individual predicted concentration, as well as the conditional weighed residuals (CWRES) versus time. Standard goodness-of-fit (GOF) plots were likewise used to assess model adequacy and aid in the model selection process by evaluating the agreement between the observed and individual predicted TXA concentration, as well as the overlay of observed and individual predicted concentration-time profiles.

Population Pharmacokinetic Modeling

Structural PK Model. A stepwise approach was followed to determine the structural model of TXA. First, peripheral compartments were sequentially incorporated to describe the distributive nature of TXA. Various absorption models were then evaluated for their ability to capture the time-dependent absorption observed for both the oral and the IM route. These included first order, first order with lag, Erlang, and Weibull absorption models. First-order elimination remained imposed for every iteration of model development based on both known physiological properties of TXA and visual inspection of the elimination phase.

Covariate PK Model. Once the base model was selected, covariate models were tested for their ability to explain observed variability in PK parameter estimates. Evaluated covariates were selected based on both physiological relevance and data availability and consistency across each of the four studies. Covariates were first screened for model inclusion based on graphical assessment of the empirical Bayes estimates (EBEs) versus covariate. Collinearity was likewise explored prior to model inclusion using both graphical and numeric assessments. Continuous covariates that were available for assessment included actual body weight, height, body mass index (BMI), and age. Internal consistency was lastly evaluated at this stage by comparing the EBEs between different TXA doses, routes of administration, and study.

Final PK Model Qualification. A non-parametric bootstrap simulation was performed to evaluate the stability and robustness of the final developed PK model. A total of 1000 datasets were generated by sampling individuals with replacement from the original dataset, and the final model was then fitted to each generated dataset. The median and 95% confidence intervals (CIs) of parameter estimates obtained from bootstrap simulation were compared with the final population PK model parameter estimates. To evaluate the validity and robustness of the final PK model, a visual predictive check (VPC) was also performed. A total of 1000 datasets were generated by simulating observations for each participant receiving fixed dosing using model estimated fixed effects and sampling from the model estimated random effect distributions. The ability of the model to reproduce the central tendency and variability of the observed data were then assessed graphically by overlaying the observed data against the 2.5th, 50th, and 97.5th percentiles of simulated concentrations.

Simulations for Regimen Exploration

The final PK model was used to perform Monte Carlo simulations for a representative virtual population of 1000 pregnant individuals per cohort randomly assigned actual body weights ranging from 60 to 120 kg. The purpose of these simulations were to (1) assess the need for weight-based dosing and (2) evaluate the effect of TXA dose and route of administration on target exposure achievement. Target exposure was defined as 10 mg/L based on a systematic review of TXA pharmacodynamic studies.[21] For the fixed dosing cohorts, a single TXA dose of 1 g IV infusion over 10 min, 1 g IM injection, or 4 g oral solution were simulated. For the weight-based dosing cohorts, a single dose of 12.5 mg/kg actual body weight IV infusion over 10 min, 12.5 mg/kg actual body weight IM injection, or 50mg/kg actual body weight oral solution were simulated. These weight-based dosing regimens were selected as the dose considered equivalent to its respective fixed dosing regimen for an 80 kg participant, the median body weight for the pooled data. An additional fixed dose cohort of 500 mg IV infusion over 10 min was likewise simulated for further investigation of therapeutic target achievement. Fixed and weight-based dosing regimens were visually compared by plotting the 5th, 50th, and 95th TXA concentration percentiles. The effect of TXA dose and route on therapeutic target achievement were numerically explored by comparing summary statistics for time to therapeutic target, time above therapeutic target, and the percentage of virtual participants achieving therapeutic target.

Results

Participants and Samples

A total of 221 participants from four different studies (NCT03863964, NCT02797119, NCT02797119, and NCT03287336) offered 1303 plasma TXA concentration measurements for model development. A summary of participant demographic data and dosing is presented in Table 1. The majority of participants included in the analysis received single fixed doses of either 1 g IV TXA (n = 97), 0.5 g IV TXA (n = 34), 1 g IM TXA (n = 26), or 4 g oral TXA (n = 30). An additional three participants received a second TXA dose of either 0.5 g (n = 1) or 1 g (n = 3), while the remaining 30 participants received weight-based dosing of either 5 mg/kg (n = 10), 10 mg/kg (n = 10), or 15 mg/kg (n = 10). On average, six PK samples were collected from each participant. The average participant age was 33 years and ranged from 22 to 47 years. The average actual body weight was 78 kg and ranged from 47 to 156 kg, while the average BMI was 31 kg/m^2 and ranged from 18 to 55.8 kg/m^2.

Population Pharmacokinetic Modeling

Structural PK Model. A two-compartment distribution model with first-order absorption for both IM and oral routes with oral lag time and first-order elimination best described the PK disposition of TXA. A summary of the resulting PK model development is presented in Table SA2. Of note, including a lag time for the oral absorption pathway reduced the OFV by 43 units for 1 additional degree of freedom. Bioavailability was also explored for both the oral and IM routes; however, the typical IM bioavailability estimate approached a value of 1 and was therefore assumed to be 100% bioavailable.

Typical PK parameter estimates were physiologically plausible and adequately described the disposition of TXA. A combination additive and proportional residual error model best described the residual error of TXA, and all random effect assumptions were maintained. BSV was not imposed on typical estimates of inter-compartmental clearance (Q), first-order oral absorption rate constant (Ka_{oral}), or first-order IM absorption rate constant (Ka_{IM}) due to high shrinkage that contributed to model overparameterization. Overall, the data was informative enough to allow for adequate assessment of covariate effect on PK disposition parameters.

Covariate PK Model. Exploratory analysis demonstrated relationships between TXA PK disposition parameters with imposed BSV—clearance (CL), central volume (Vc), and peripheral volume (Vp)—and covariates of BMI and actual body weight. The relationship

Table 1. Participant Demographic and Dosing Summary Stratified by Study

Study	NCT03863964	NCT02797119	NCT04274335	NCT03287336	Total
Count	20	89	82	30	221
Age (years)					
Mean (SD)	37.8 (3.99)	34.2 (4.65)	30.9 (4.31)	31.9 (5.14)	33.0 (4.98)
Median	37.5	34.0	30.0	32.5	33.0
[Min, Max]	[31.0, 47.0]	[23.0, 44.0]	[22.0, 41.0]	[23.0, 41.0]	[22.0, 47.0]
Body weight (kg)					
Mean (SD)	83.1 (24.0)	83.6 (16.3)	75.4 (12.4)	92.8 (21.7)	81.7 (17.6)
Median	76.7	78.0	74.5	86.5	78.0
[Min, Max]	[58.5, 156]	[59.0, 148]	[47.0, 111]	[59.5, 148]	[47.0, 156]
Height (cm)					
Mean (SD)	157 (20.6)	165 (7.35)	158 (6.22)	164 (8.55)	161 (9.73)
Median	160	165	158	163	162
[Min, Max]	[72.6, 173]	[150, 185]	[142, 171]	[150, 183]	[72.6, 185]
BMI (kg/m^2)					
Mean (SD)	30.5 (7.27)	30.7 (5.30)	30.2 (4.62)	34.7 (8.45)	31.0 (5.93)
Median	28.6	29.4	30.0	31.2	30.0
[Min, Max]	[21.0, 45.6]	[22.9, 50.0]	[18.0, 40.0]	[23.2, 55.8]	[18.0, 55.8]
# PK samples					
Mean (SD)	10 (3)	4 (1)	8 (1)	6 (1)	6 (2)
Median	9	4	8	6	6
[Min, Max]	[4, 13]	[1, 6]	[5, 9]	[2, 6]	[1, 13]
Dosing					
IV					
Weight based					
5 mg/kg	0	0	0	10	10
10 mg/kg	0	0	0	10	10
15 mg/kg	0	0	0	10	10
Fixed					
0.5 g	0	34	0	0	34
1 g	20	51	26	0	97
1.5 g	0	1	0	0	1
2 g	0	3	0	0	3
IM					
Fixed					
1 g	0	0	26	0	26
Oral					
Fixed					
4 g	0	0	30	0	30

between actual body weight and these three disposition parameters appeared visually stronger as compared with BMI. Actual body weight was therefore selected for model inclusion based on this trend and the clinical relevance of weight-based dosing that would be further explored with the developed model. No other covariates demonstrated a clear relationship when visually inspecting the EBEs versus covariate plots. Although BSV was not imposed on Q due to high shrinkage, this parameter was likewise allometrically scaled with body weight using the same exponent as the one applied to CL. The effect of actual body weight (WT) on CL, Vc, Q, and Vp was therefore included using the following allometric scaling equation:

$$P_i = P_{pop} \times \left(\frac{WT}{80}\right)^{\text{exponential}} \times e^{\eta i}$$

where P_i is the individual PK parameter value for participant i; P_{pop} is the typical population value for the PK parameter for a reference participant weighing 80 kg; exponential is the allometric scaling power exponent; and η_i the individual deviation from P_{pop}. Exponents were initially estimated separately for each disposition parameter and then collectively within their respective categories (clearance or volume terms) if the independent estimates were qualitatively similar. For clearance parameters (CL and Q), an exponent of 0.89 was estimated. For volume parameters, the exponents were estimated as 0.45 for Vc and 0.41 for Vp, resulting in a final pooled estimate of 0.44 that was retained. Inclusion of each pooled estimate reduced the OFV by 33.1, 12.6, 6.2, and 4.1 units when included on CL, Vc, Vp, and Q, respectively. Inclusion of WT as a covariate reduced BSV on CL from 37% to 33%,

Table 2. Final PK Model Parameter Estimates

Parameter	Description	Final model Estimate	Bootstrap (N = 1000)[a] Median [95% CI]
Population PK parameters			
CL^b	Total body clearance (L/h/80 kg)	8.59	8.55 [8.07, 9.08]
Vc^b	Central volume of distribution (L/80 kg)	10.7	10.6 [8.38, 13.9]
Q^b	Inter-compartmental clearance (L/h/80 kg)	28.9	28.1 [19.6, 47.2]
Vp^b	Peripheral volume of distribution (L/80 kg)	15.0	15.1 [13.2, 16.9]
Ka_{oral}	First-order absorption rate constant for oral formulation (1/h)	0.18	0.18 [0.16, 0.32]
Ka_{IM}	First-order absorption rate constant for intramuscular formulations (1/h)	2.31	2.36 [1.89, 3.10]
F_{oral}	Oral bioavailability	0.56	0.54 [0.38, 0.73]
$Tlag_{oral}$	Oral absorption lag time (h)	0.16	0.18 [0.12, 0.31]
Covariates			
Weight on CL and Q	Allometric scaling exponent to describe the effect of weight on clearance	0.89	0.88 [0.57, 1.18]
Weight on V_c and V_p	Allometric scaling exponent to describe the effect of weight on volume	0.44	0.45 [0.25, 0.73]
Between-subject variability (BSV)			
ω_{CL}	BSV on CL (%CV)	32.4 [shrinkage: 12%]	32.3 [27.6, 37.4]
ω_{Vc}	BSV on Vc (%CV)	59.5 [shrinkage: 30%]	57.9 [38.9, 76.6]
ω_{Vp}	BSV on Vp (%CV)	46.4 [shrinkage: 28%]	46.6 [32.5, 58.2]
ω_{Foral}	BSV on F_{oral} (%CV)	44.8 [shrinkage: 67%]	43.7 [25.1, 58.1]
$\omega_{Tlagoral}$	BSV on $Tlag_{oral}$ (%CV)	64.6 [shrinkage: 69%]	64.0 [32.1, 138]
Within-subject variability (WSV)			
$\sigma_{additive}$	Additive residual error (mg/L)	0.67	0.69 [0.52, 0.88]
$\sigma_{proportional}$	Proportional residual error (%)	27.2	26.7 [22.7, 29.5]

[a] Final model bootstrap estimates and 95% CI are reported as median and 2.5th-97.5th percentiles of the parameter estimates.
[b] Final model parameter estimates for population clearances and volumes of distributions are standardized to a typical subject of 80 kg, where $CL_i = 8.59\ L/h \cdot (\frac{WT}{80})^{0.89} \cdot e^{\eta_{CLi}}$; $Vc_i = 10.7L \cdot (\frac{WT}{80})^{0.44} \cdot e^{\eta_{Vci}}$; $Q_i = 28.9\ L/h \cdot (\frac{WT}{80})^{0.89}$; $Vp_i = 15.0\ L \cdot (\frac{WT}{80})^{0.44} \cdot e^{\eta_{Vpi}}$.

and did not explain substantial variability in volume terms.

Final PK Model Qualification. Final population PK parameter estimates are reported in Table 2. For a typical participant weighing 80 kg, the CL, Vc, Q, and Vp were estimated to be 8.59 L/h, 10.7 L, 28.9 L/h, and 15.0 L, respectively. The typical first-order absorption rate constants for the oral and IM formations were 0.18 L/h and 2.31 L/h, respectively. The typical oral bioavailability (F_{oral}) was estimated to be 56%, while 0.16 h was the estimated typical oral absorption lag time ($Tlag_{oral}$). The estimated BSV on CL, Vc, Vp, F_{oral}, and $Tlag_{oral}$ were 32.4%, 59.5%, 46.4%, 44.8%, and 64.6%, respectively. High shrinkage was observed on parameters F_{oral} and $Tlag_{oral}$ (67% and 69%, respectively). BSV remained imposed on these parameters, however, due to their important contribution in differentiating the observed oral bioavailability and absorption lag time, and the lack of intention to assess covariate effects on these parameters.

The final PK model provided a reasonable characterization of the data, as illustrated by the diagnostic GOF plots (Figure 1, Figure SA2). The plot of individual predicted versus observed concentration of TXA revealed that observations were evenly distributed around the line of identity, indicating that the final population model adequately described the range of concentrations from all included studies. Residual plots further support adequacy of the structural model selected. The weighted population residuals versus time plot demonstrate no obvious trends around the zero line from times ranging from 0 to approximately 12 h post-dose. Underprediction can be observed for PK observations at 24-h post-dose. However, this was deemed to be a reasonable deviation as concentrations at this time are well below the therapeutic target. Bootstrap simulations used to qualify the final model achieved a 100% successful refitting rate, with all replicates successfully converging. These simulations likewise confirmed that PK parameters were estimated with high precision, as demonstrated by the resulting narrow confidence interval (Table 2). The results of the VPC also highlighted a strong agreement between the predicted and observed concentrations (Figure 2). Of note, the final model was able to reliably capture the variability in the data as the distribution of model predicted concentrations closely align with the observed data points. As demonstrated by the weighted residual plot, underprediction is appreciated

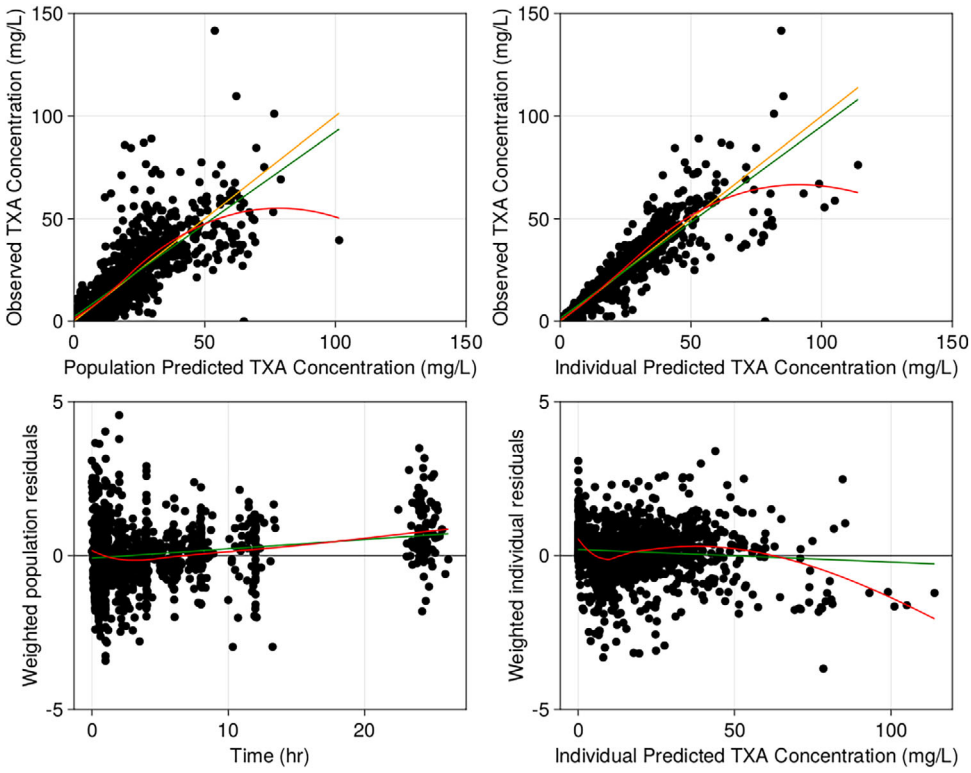

Figure 1. Goodness-of-fit plots for the final PK model. Yellow lines are the lines of identity, green lines are ordinary least square regression fits, and red lines are local polynomial regression fits.

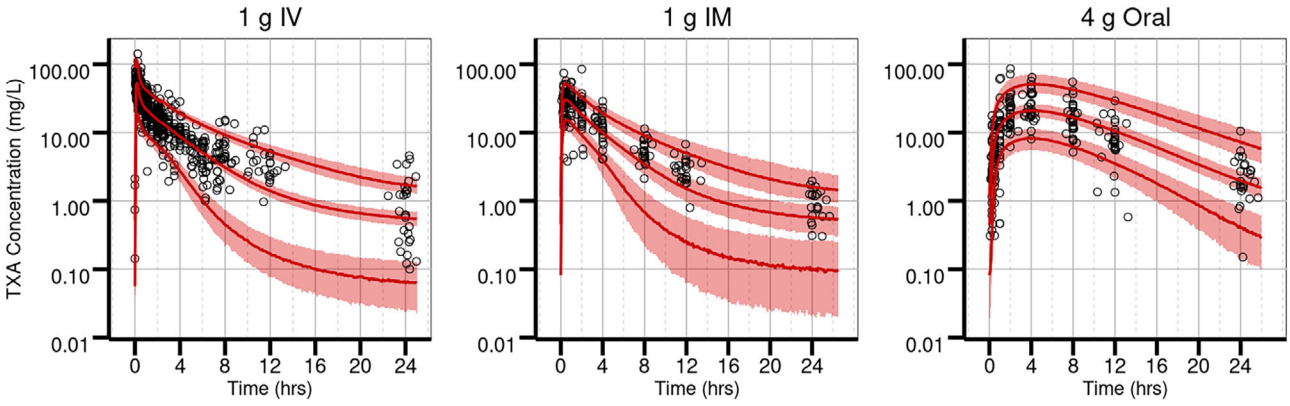

Figure 2. Visual predictive check for the developed sequential population PK model. Black open circles are the observed concentrations, solid red lines are the 5th, 50th, and 95th quantiles of the simulated data, shaded red bands are the 95% visual prediction interval for each simulated quantile.

at 24 h post-dose, but this was deemed to be reasonable from a fit-for-purpose standpoint. Overall, the final developed model describes the four study populations adequately and can be reliably leveraged to explore dosing strategies for each of the three administration routes.

Simulations for Regimen Exploration

Visual comparison of fixed and weight-based dosing regimens are presented in Figure 3. For all routes of administration, actual weight-based dosing regimens result in near identical exposure profiles to their fixed dosing counterpart. Only minor differences can be observed for the median time at which TXA concentrations fall below the target plasma concentration between the 1 g IV and 12.5 mg/kg IV cohort comparison. The assessment of fixed dosing regimens to achieve and sustain therapeutic targets is presented in Table 3. Of note, the 500 mg IV, 1 g IV, and 1 g IM regimens reach >99% target achievement, while the 4 g oral regimen achieved therapeutic targets in approximately 89% of simulated participants. On average, the therapeutic tar-

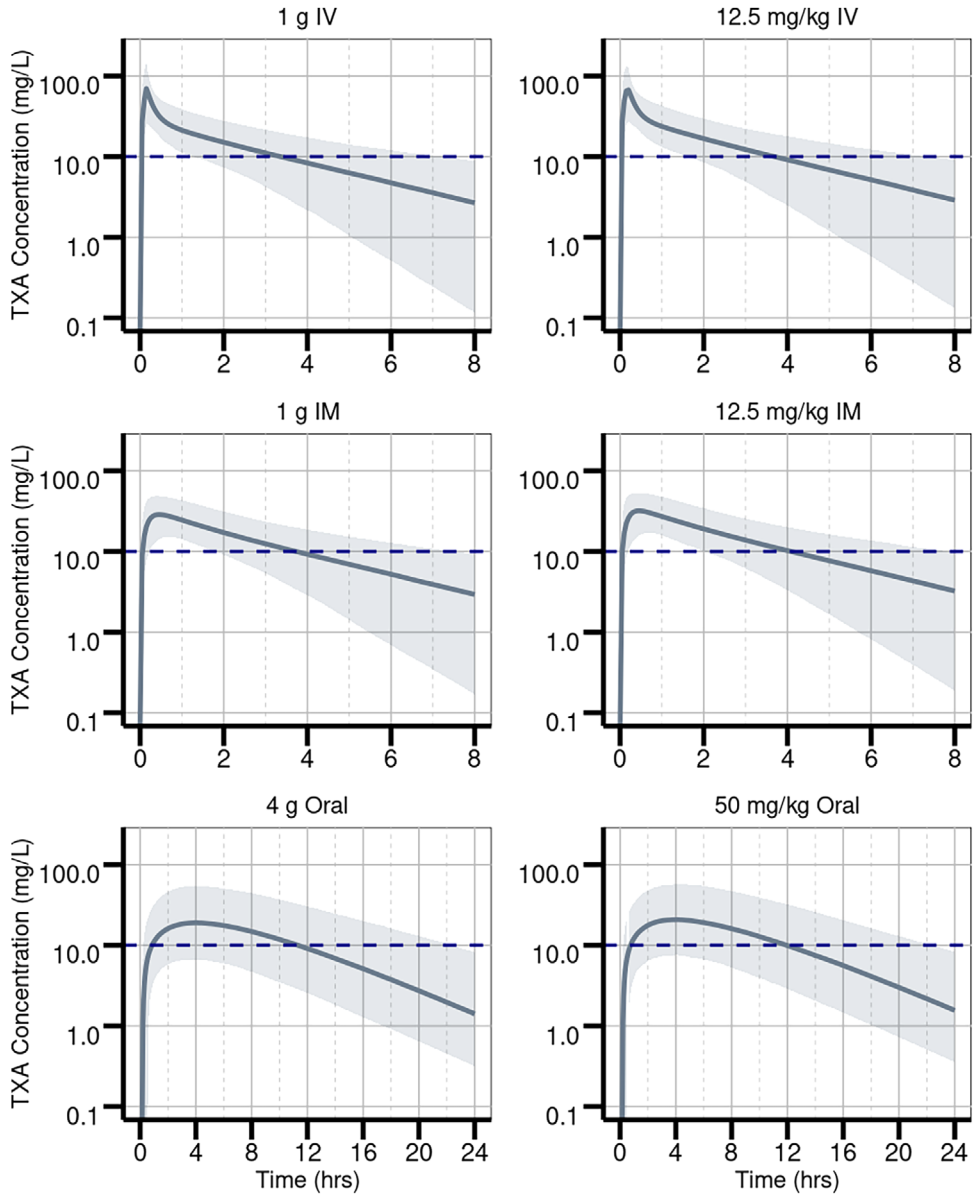

Figure 3. Simulation to demonstrate target exposure achievement with fixed versus weight-based dosing. The dotted blue line represents the TXA target exposure, the solid grey line represents the 50th simulated concentration percentile, and the shaded region represents the 5th to 95th simulated concentration percentile.

Table 3. Simulation Result Summary

Route	Intravenous		Intramuscular	Oral
Dose	500 mg	1 g	1 g	4 g
% Achieving target of 10 μg/mL	99.15%	99.98%	99.89%	89.29%
Time to target (h)				
Mean (SD)	0.05 (0.02)	0.03 (0.01)	0.08 (0.06)	0.96 (0.67)
Median	0.04	0.02	0.06	0.77
[Min, Max]	[0.01, 0.16]	[0.01, 0.16]	[0.02, 0.39]	[0.17, 3.32]
Time above target (h)				
Mean (SD)	1.31 (0.79)	3.56 (1.50)	3.85 (1.50)	11.3 (4.75)
Median	1.11	3.34	3.61	11.1
[Min, Max]	[0.27, 4.16]	[0.86, 8.85]	[1.24, 9.17]	[1.55, 23.2]

get was reached at 3, 1.8, 4.8, and 58 min for the 500 mg IV, 1 g IV, 1 g IM, and 4 g oral cohorts, respectively. The therapeutic target was then sustained, on average, for 1.31, 3.56, 3.85, and 11.3 h for the 500 mg IV, 1 g IV, 1 g IM, and 4 g oral cohorts, respectively.

Discussion

A two-compartment distribution model with first-order absorption for both IM and oral routes with oral lag time and first-order elimination most adequately described TXA PK. This aligns with prior PK characterization studies in both healthy and pregnant individuals.[19,22,23] Actual body weight was the only assessed covariate to significantly improve model fit. There were no significant differences in PK when comparing study location, TXA dose, or TXA route of administration. Although actual body weight was determined to be a significant covariate, the estimated exponent to describe the steepness of the relationship between weight and volume revealed a shallower relationship than traditional allometric scaling.[24] Additionally, inclusion of actual body weight only reduced the BSV of total body clearance from 37% to 33%, meaning that although body weight was a statistically significant covariate it did not explain a substantial amount of the observed variability. This demonstrates that, for the range of actual body weights included in the analysis (47-156 kg), differences in body weight are unlikely to explain clinically significant differences in TXA exposure. This was further demonstrated by simulating representative virtual populations of pregnant individuals and comparing the range of TXA exposures for fixed and weight-based dosing regimens (Figure 3). In cases where body weight explains substantial variability, we would expect to observe a narrowing of the exposure interval for the weight-based dosing simulation. In this exercise, however, the predicted 95% exposure interval was near identical between fixed and weight-based dosing. This exercise therefore supports the current guideline recommendations to use fixed TXA dosing in pregnant individuals.

There are three key takeaways from the simulations to assess target exposure achievement for different TXA doses and routes of administration. The first is that IM TXA is a viable alternative to IV administration. This finding is also supported by prior research conducted in healthy volunteers.[19] For a 1 g dose of TXA, both IV and IM routes of administration will achieve target TXA exposures in >99% of individuals. Differences in the concentration–time profile for IV and IM administration are minimal, with the average time to target exposure being approximately 2 and 5 min for a 1 g dose, respectively. However, given the full-term uterus has up to 800 mL of blood supply per minute circulating to it, in an acute hemorrhage, minutes may make a difference between severe or average blood loss.[25,26]

The second takeaway is that for both the IV and IM routes of administration the target TXA exposure is sustained in most participants for at least 1 h. By 3 h, half of the participants continue to have a sustained plasma concentration above the target. The IM route does elicit exposures above target for a marginally longer duration (approximately 17 min, on average). This finding likewise provides insight into the clinical need for administering an additional TXA dose with each regimen, as half of the patients would remain adequately dosed for up to 3 h regardless of the administration route. Overall, this research supports that IM administration of TXA will result in similar exposure profiles to IV TXA administration.

The final takeaway is that the characterization of the oral formulation can guide dosing strategies in pregnant populations for other indications or in regions where IV and IM formulations are not readily available. Oral TXA administration is not an optimal choice for the treatment of PPH, as demonstrated by the delayed time to achieve target exposures (~1 h) when compared to IV and IM routes (~2 or 5 min, respectively). However, in healthcare settings where IV or IM TXA is not readily available, understanding the time to target achievement is critical for planning and optimizing dosing regimens. Additionally, these findings offer valuable insights into the broader PK profile of TXA in pregnant individuals, which could help guide dosing and monitoring strategies for other indications. While oral TXA does not achieve timely target exposures compared to IV or IM routes, the oral formulation does sustain the therapeutic target concentration for much longer (~11 h, on average) compared to the IV and IM formulation (~4 h, on average). This information may allow clinicians to make more informed decisions about its timing and potential applications in non-acute indications where immediate therapeutic levels are not required.

There are several limitations of this study that warrant further discussion. First, bioanalysis differences across the four studies may inflate the observed unexplained variability. A comparison of EBEs by study did, however, indicate no substantial differences in the distribution of PK parameters across participants. Additionally, the retrospective nature of this study means that data collection was not standardized across the four studies. This limits the extent of the covariate analysis able to be performed. For example, prior studies have identified renal function as a significant covariate effect on clearance.[22] This information was not collected for all four studies included, and therefore could not be included in this analysis. Given that renal function is known to significantly influence the total

body clearance of TXA, the absence of this data leaves an additional gap in the explanation of BSV in TXA clearance. Additionally, not all studies included urinary levels of TXA and therefore the contribution of renal clearance to total body clearance could not be estimated. Although this may be considered a limitation, the model developed served its purpose to make an inference on dosing in pregnant individuals.

Moving forward, this model could be implemented in future research by incorporating a pharmacodynamic (PD) component, like those that assessed maximum lysis or other PD endpoints.[22] Expanding this research would allow one to characterize the exposure–response relationship in a diverse pregnant population, including those of varying disease states and demographic factors known to influence drug response. This could provide more confidence in answering clinical questions around dosing and monitoring strategies in this population. Additionally, with increased availability of real-world evidence the learnings of this research could be expanded to enhance our understanding of TXA's variability in response across different clinical environments and populations. Overall, this study provides a comprehensive understanding of TXA PK in pregnant and postpartum individuals. Simulations support current FIGO guidelines for fixed dosing of TXA in PPH, however additional research may be needed to optimize current recommendations.

Conclusion

This study provides a comprehensive pharmacokinetic characterization of TXA in a diverse population of pregnant and postpartum individuals, affirming the current WHO recommendations and FIGO guidelines for fixed dosing in PPH. This study additionally supports the idea that IM administration is a viable alternative to IV administration, achieving similar exposure profiles.

Conflicts of Interest

Jogarao V. S. Gobburu is a co-founder of Pumas AI, the company that developed the software, Pumas, which was used to develop this population PK model and perform simulations.

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Data Sharing

The data that support the findings of this study are available upon reasonable request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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Supplemental Information

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