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Tranexamic acid through intravenous, intramuscular and oral routes: an individual participant data meta-analysis of pharmacokinetic studies in healthy volunteers

Short title: Pharmacokinetics of tranexamic acid in healthy volunteers

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ABSTRACT

Background: Tranexamic acid (TXA) is an antifibrinolytic drug that reduces surgical blood loss and death due to bleeding after trauma and post-partum haemorrhage. One key issue for treatment success is early administration. While usually given intravenously, oral and intramuscular use would be useful in specific circumstances. Therefore, an understanding of TXA pharmacokinetics when given via different routes is valuable. The aim of this study was to perform an individual participant data meta-analysis of pharmacokinetic studies with TXA given to healthy volunteers via different routes.

Methods: We searched the following databases: PubMed, Web of Science, Wiley Online Library, Elsevier Science Direct and J-STAGE. Individual subject data were extracted when available, otherwise arithmetic means were used. A population pharmacokinetic model was developed using nonlinear mixed effect modelling.

Results: Seven studies were included in the analysis with data from 10 patients for the IV route, 6 patients for the IM route and 114 patients for the oral route. The pharmacokinetics was ascribed to

a two-compartment model and the main covariate was allometrically scaled bodyweight. Oral and IM bioavailabilities were 46% and 105%, respectively. For a 70 kg bodyweight, 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.

Conclusions: Larger well-designed studies are needed to describe the pharmacokinetics of TXA when given IM or as an oral solution before these can be recommended as alternatives to IV.

Keywords: Tranexamic acid; pharmacokinetics; individual participant data meta-analysis; healthy volunteer; intravenous; intramuscular; oral.

INTRODUCTION

Tranexamic acid (TXA) is a molecular analogue of lysine that inhibits the enzymatic breakdown of fibrin blood clots by competing with fibrin for the lysine binding sites in plasminogen [1], thereby reducing bleeding in a number of clinical situations such as surgery [2], menorrhagia [3], acute upper gastrointestinal bleeding [4] or haemoptysis [5]. It is currently licenced as an antifibrinolytic drug for haemorrhagic conditions as high-bleeding risk surgery or gastrointestinal bleeding. Large-scale clinical trials have also demonstrated that intravenous administration of TXA safely reduces death due to bleeding in patients with trauma and post-partum haemorrhage [6-8]. In both situations, most deaths occur soon after bleeding onset and treatment delay reduces the survival benefit [9]. Early initiation of treatment is therefore a key issue in management, and the intravenous route is the unique route currently used in these urgent situations. However, qualified personnel for intravenous administration is not always available in a timely manner, securing IV access can be difficult in shocked patients with collapsed veins and some situations such as battlefields for the war wounded are difficult to reconcile with the use of a venous approach. Despite TXA is available for oral (tablets

or oral solution) and intravenous use, there has been little research into different routes of administration. Giving an oral solution (as opposed to tablets) may reduce the time needed to reach therapeutic levels in patients able to swallow (post-partum haemorrhage women for example) while intramuscular injection would be easier and faster to administer and would require less training than IV use for injured or isolated patients (battlefield wounded soldiers or trauma patients for example). Although the pharmacokinetics of TXA after intravenous administration has been well studied in bleeding conditions such as paediatric or adult cardiac surgery and trauma [10-15], the pharmacokinetics of TXA through other administration routes is poorly described. Since data through different administration routes are available in healthy volunteers, the aim of the present study was to propose an individual participant data meta-analysis of pharmacokinetic studies with tranexamic acid in healthy volunteers.

METHODS AND ANALYSIS

This individual participant data meta-analysis protocol was prepared according to the Preferred Reporting Items for Systematic Review and Meta-Analyses of individual participant data (PRISMA-IPD) guidelines [16].

Eligibility criteria

Eligible studies were all trials including healthy human volunteers administered tranexamic acid by any administration route for systemic exposure with measurement of plasma tranexamic acid concentrations. The specific criteria were:

Population: studies examining healthy humans (both adults and children) were eligible.

Interventions: Tranexamic acid by any route of administration aimed at systemic exposure.

Comparators: None or any.

Outcome: The outcome of interest is the description of the drug pharmacokinetics or plasma concentrations.

Study design: There were no restrictions by type of design since the main outcome is a drug plasma concentration.

Time: Studies of any duration conducted at any time.

Other: Unpublished and published studies written in any language were included.

Search strategy and study selection

The search strategy was designed and conducted by the primary investigator and was independently reviewed by a second author, utilizing several databases from inception to January 22, 2019. The databases included PubMed, Web of Science, Wiley Online Library, Elsevier Science Direct and J-STAGE. Controlled vocabulary supplemented with keywords was used to search for tranexamic acid pharmacokinetic data in healthy volunteers. A draft MEDLINE search strategy was: "tranexamic acid" AND (pharmacokinetics OR absorption OR excretion OR distribution OR plasma concentration) AND (healthy subjects OR volunteers).

Data collection

When available, individual subject data were obtained, otherwise arithmetic means were used and considered as a typical subject record. Data extraction was performed directly from tables or from figures with plotDigitizer. When individual demographics were not available, bodyweight or age values were set to the reported mean value, otherwise age was arbitrarily set at 30-year-old;

bodyweight at 75 kg for studies conducted in Europe or 62 kg for studies conducted in China. Default sex was set to male.

Pharmacokinetic modeling

Tranexamic acid time-courses were analyzed using the nonlinear mixed effect modelling software program Monolix 2018R2 (www.lixoft.eu) [17]. Parameters were estimated by computing the maximum likelihood estimator of the parameters without any approximation of the model (no linearization) using the stochastic approximation expectation maximization algorithm combined to a Markov Chain Monte Carlo procedure. To ensure full convergence the iteration number was fixed to 2000. Different error models were investigated (i.e. additive, proportional or combined error models) to describe residual variabilities (ε), and the between-subject variabilities (BSV or η) were ascribed to an exponential model. The Bayesian information criterion (BIC) was used to test different hypotheses regarding the model, i.e. i) covariate effect(s) on pharmacokinetic parameter(s), ii) residual variability model and iii) structure of the variance-covariance matrix for the ω parameters. The main demographic characteristic likely plausible for affecting pharmacokinetics for which data were available was bodyweight, which effect was evaluated. Parameter estimates were standardized for a mean standard bodyweight of 70 kg using an allometric model: $P_i = P_{STD} \times (COV_i/70)^{PWR}$ where P_{STD} is the standard value of parameter and P_i and COV_i are the parameter and covariate values of the i^{th} individual. The PWR exponents may be estimated from the data. However, for bodyweight, allometric scaling theory dictates that these are typically 0.75 and 1 for clearance and volumes terms respectively [18]. The goodness-of-fit of each model was evaluated by visual inspection of the individual concentration-time courses, the observed-predicted (population and individual) concentration scatter plots and the prediction-corrected visual predictive checks.

RESULTS

Study characteristics

PRISMA flow diagram of study selection is depicted in Figure 1. Our search strategy identified 71 unique citations. After screening titles and abstracts, 51 studies were excluded because no pharmacokinetic data was reported and 10 studies were excluded because the study population was not healthy human volunteers. A total of 10 studies were therefore deemed eligible for full text retrieval [19-28]. Among those, 1 study was excluded for wrong participant population [19]; 1 because the study drug was a prodrug [21] and another one because tranexamic acid was used for local treatment [20]. We therefore included 7 studies published between 1974 and 2012, whose characteristics are shown in Table 1. Six studies were written in English and one in Japanese [27], which was translated using Google Traduction.

Data available

Data were available from 10 participants in 4 studies for the IV route, 6 participants in 2 studies for the IM route and 114 participants in 6 studies for the oral route. Moore *et al.* also investigated the pharmacokinetics of modified-release tablets but only data from the immediate release formulation were exploited in the present study [24]; similarly Sindet-Pedersen was also interested in the use of local application of TXA in mouth rinsing solutions [28] which was not considered for this study. A total of 5 participants received several doses from different routes in cross-over design studies. Therefore, data from 125 different participants were used for the final analysis. All studies but one assessed the pharmacokinetics after a single-dose exposure. In those studies, doses were in the range 0.25-2 g for the oral route and 0.5-1 g for the IM and IV routes. In the last study, participants were exposed to a first oral TXA 1.3 g dose followed 36 hours later by a multiple dose, 1.3-g every 8-

hour oral dosage regimen for 5 additional days [24]. Sampling times were up to 6-32 hrs after IV administration, 6-8 hrs for the intramuscular route and 6-36 hrs for the oral route.

Pharmacokinetic modelling

The pharmacokinetics was ascribed to a two-compartment open model with first-order absorption. The parameters of the model were oral and intramuscular absorption constants (ka_{PO} and ka_{IM}, respectively) and bioavailabilities (F_{PO} and F_{IM}, respectively), the elimination clearance CL, the inter-compartmental clearance Q, the volume of distribution of the central compartment Vc and the volume of distribution of the peripheral compartment Vp. The equations were as follows:

$$dS/dt = -ka_S \times S$$

$$dA_1/dt = ka_S \times S - k_{10} \times A_1 - k_{12} \times A_1 + k_{21} \times A_2$$

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

where A_1 and A_2 are the amounts of drug in the compartments; S is the site of absorption (PO or IM, with S equals 0 for the IV route); k_{10}=CL/Vc, k_{12}=Q/Vc and k_{21}=Q/Vp. Then the drug concentration in the central compartment is

$$C = F_S \times A_1/Vc$$

Between subject variabilities were estimated for F_{PO}, ka_{PO}, ka_{IM}, CL and Vc using an exponential model and the residual variability was estimated for each of the 7 studies using a proportional error model. The goodness-of-fit of the model was improved when the parameters were allometrically normalized for bodyweight (decrease of BIC of 10 units). For a 70 kg bodyweight individual, 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. Oral and IM bioavailabilities were 46% and 105%, respectively. The relative standard error of the estimates was <14%. Table 2 shows the final population pharmacokinetic estimates. Figure 2, 3 and 4 show representative pharmacokinetic time-courses for 8 participants, observed *vs* predicted concentrations and prediction-corrected visual predictive check plots, respectively.

DISCUSSION

This meta-analysis of individual participant data reports the population pharmacokinetics of tranexamic acid in healthy volunteers after oral, intramuscular or intravenous administration. As previously reported in studies in adult surgery or trauma patients, the pharmacokinetics was ascribed a two-compartment model and bodyweight was the main covariate affecting the pharmacokinetics [12-14, 29-31]. Attempts with 1-compartment models always provided models with poorer performance than 2-compartment models. For the intramuscular and oral routes, the estimated bioavailabilities were 105% and 46%, respectively, demonstrating an excellent and complete intramuscular absorption while half of the drug is eliminated before systemic passage through the digestive system. Taking into account the confidence interval of the estimate that includes 100%, it can be considered that IM bioavailability does not exceed the maximal 100% theoretical value. Values previously reported in adults for elimination clearance, the main pharmacokinetic parameter of interest, were in the range 4.8-7.9 $L.h^{-1}$ for patients undergoing

cardiac surgery or trauma patients [12-14, 29-31], which is consistent with the clearance documented here for healthy volunteers.

Hence, this meta-analysis summarizes the pharmacokinetics of TXA in healthy volunteers. The risk of bias is limited since the reported outcome in each individual study is a drug concentration. However, limitations are related to the small sample size, especially for the IM and IV routes, to the lack of individual pharmacokinetic data or of complete demographic data in some studies. This may have impacted the identification of covariates of interest and a precise estimation of bioavailabilities or between-subject variability for some parameters. Between-subject variability may also be overestimated when the inter-study variability for individual pharmacokinetic parameters is not taken into account [32], but results therefore show the most pessimistic estimations. Furthermore, healthy volunteers were only men for the IV and IM routes and almost only women for the oral route, with a limited range in age and bodyweight. We had no information on renal function in the volunteers while TXA is fully excreted by the kidneys and renal function has already been shown to impact the pharmacokinetics in other contexts [29, 30]. In addition, studies were performed in several different countries in Europe, USA, China or Japan and the small sample size did not allow to perfectly assess the effects of ethnicity, which is however rather expected for drug with hepatic metabolism. Finally, for the oral route, only studies using tablets were published, with sometime the use of immediate- or delayed-release tablets. In certain conditions, the early administration of the drug is a critical issue. Knowing that an oral solution is also commercialized in several countries, clinical studies to assess the pharmacokinetics of this formulation would be of interest since the absorption is expected to be quicker.

In conclusion, larger well-designed studies are needed to better describe the pharmacokinetics of TXA after IM use or when given as an oral solution before these routes can be recommended as alternatives to IV use.

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REFERENCES

1. McCormack P.L. Tranexamic acid: a review of its use in the treatment of hyperfibrinolysis. Drugs. (2012) **72** 585-617.

2. Ker K., Edwards P., Perel P., Shakur H., Roberts I. Effect of tranexamic acid on surgical bleeding: systematic review and cumulative meta-analysis. BMJ. (2012) **344** e3054.

3. Bryant-Smith A.C., Lethaby A., Farquhar C., Hickey M. Antifibrinolytics for heavy menstrual bleeding. Cochrane Database Syst. Rev. (2018) **4** CD000249.

4. Bennett C., Klingenberg S.L., Langholz E., Gluud L.L. Tranexamic acid for upper gastrointestinal bleeding. Cochrane Database Syst. Rev. (2014) **11** CD006640.

5. Prutsky G., Domecq J.P., Salazar C.A., Accinelli R. Antifibrinolytic therapy to reduce haemoptysis from any cause. Cochrane Database Syst. Rev. (2016) **11** CD008711.

6. Collaborators W.T. Effect of early tranexamic acid administration on mortality, hysterectomy, and other morbidities in women with post-partum haemorrhage (WOMAN): an international, randomised, double-blind, placebo-controlled trial. Lancet (2017) **389** 2105-2116.

7. CRASH-2 Collaborators, Roberts I., Shakur H., Afolabi A., Brohi K., Coats T. et al. The importance of early treatment with tranexamic acid in bleeding trauma patients: an exploratory analysis of the CRASH-2 randomised controlled trial. Lancet. (2011) **377** 1096-1101, e1-2.

8. CRASH-2 trial Collaborators, Shakur H., Roberts I., Bautista R., Caballero J., Coats T. et al. 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. Lancet (2010) **376** 23-32.

9. Gayet-Ageron A., Prieto-Merino D., Ker K., Shakur H., Ageron F.X., Roberts I. et al. Effect of treatment delay on the effectiveness and safety of antifibrinolytics in acute severe haemorrhage: a meta-analysis of individual patient-level data from 40 138 bleeding patients. Lancet (2018) **391** 125-132.

10. Gertler R., Gruber M., Grassin-Delyle S., Urien S., Martin K., Tassani-Prell P. et al. Pharmacokinetics of tranexamic acid in neonates and infants undergoing cardiac surgery. Br. J. Clin. Pharmacol. (2017) **83** 1745-1757.

11. Grassin-Delyle S., Couturier R., Abe E., Alvarez J.C., Devillier P., Urien S. A practical tranexamic acid dosing scheme based on population pharmacokinetics in children undergoing cardiac surgery. Anesthesiology (2013) **118** 853-862.

12. Grassin-Delyle S., Theusinger O.M., Albrecht R., Mueller S., Spahn D.R., Urien S. et al. Optimisation of the dosage of tranexamic acid in trauma patients with population pharmacokinetic analysis. Anaesthesia. (2018) **73** 719-729.

13. Grassin-Delyle S., Tremey B., Abe E., Fischler M., Alvarez J.C., Devillier P. et al. Population pharmacokinetics of tranexamic acid in adults undergoing cardiac surgery with cardiopulmonary bypass. Br. J. Anaesth. (2013) **111** 916-924.

14. Dowd N.P., Karski J.M., Cheng D.C., Carroll J.A., Lin Y., James R.L. et al. Pharmacokinetics of tranexamic acid during cardiopulmonary bypass. Anesthesiology. (2002) **97** 390-399.

15. Wesley M.C., Pereira L.M., Scharp L.A., Emani S.M., McGowan F.X. Jr., DiNardo J.A. Pharmacokinetics of tranexamic acid in neonates, infants, and children undergoing cardiac surgery with cardiopulmonary bypass. Anesthesiology. (2015) **122** 746-758.

16. Stewart L.A., Clarke M., Rovers M., Riley R.D., Simmonds M., Stewart G. et al. Preferred Reporting Items for Systematic Review and Meta-Analyses of individual participant data: the PRISMA-IPD Statement. JAMA. (2015) **313** 1657-1665.

17. Kuhn E., Lavielle M. Maximum likelihood estimation in nonlinear mixed effects models. Comput. Stat. Data Analysis. (2005) **49** 1020-1038.

18. Anderson B.J., Holford N.H. Mechanism-based concepts of size and maturity in pharmacokinetics. Annu. Rev. Pharmacol. Toxicol. (2008) **48** 303-332.

19. Benoni G., Björkman S., Fredin H. Application of Pharmacokinetic Data from Healthy Volunteers for the Prediction of Plasma Concentrations of Tranexamic Acid in Surgical Patients. Clin. Drug Investig. (1995) **10** 280-287.

20. Almer S., Andersson T., Strom M. Pharmacokinetics of tranexamic acid in patients with ulcerative colitis and in healthy volunteers after the single instillation of 2 g rectally. J. Clin. Pharmacol. (1992) **32** 49-54.

21. Svahn C.M., Schannong M., Stenberg U., Widlund L. Absorption of tranexamic acid as a prodrug in healthy volunteers. Arzneimittelforschung. (1988) **38** 735-738.

22. Chang Q., Yin O.Q., Chow M.S. Liquid chromatography-tandem mass spectrometry method for the determination of tranexamic acid in human plasma. J. Chromatogr B. Analyt. Technol. Biomed. Life Sci. (2004) **805** 275-280.

23. Eriksson O., Kjellman H., Pilbrant A., Schannong M. Pharmacokinetics of tranexamic acid after intravenous administration to normal volunteers. Eur. J. Clin. Pharmacol. (1974) **7** 375-380.

24. Moore K.A., Morin I., Marenco T., Lavigne J.R., Morelli G. Pharmacokinetic studies in women of 2 novel oral formulations of tranexamic acid therapy for heavy menstrual bleeding. Am. J. Ther. (2012) **19** 190-198.

25. Pilbrant A., Schannong M., Vessman J. Pharmacokinetics and bioavailability of tranexamic acid. Eur. J. Clin. Pharmacol. (1981) **20** 65-72.

26. Puigdellivol E., Carral M.E., Moreno J., Pla-Delfina J.M., Jane F. Pharmacokinetics and absolute bioavailability of intramuscular tranexamic acid in man. Int. J. Clin. Pharmacol. Ther. Toxicol. (1985) **23** 298-301.

27. Sano M., Hakusui H, Kojima C, Akimoto T. Absorption and Excretion of Tranexamic Acid following Intravenous, Intramuscular and Oral Administrations in Healthy Volunteers. Japanese Journal of Clinical Pharmacology and Therapeutics. (1976) **7** 375-382.

28. Sindet-Pedersen S. Distribution of tranexamic acid to plasma and saliva after oral administration and mouth rinsing: a pharmacokinetic study. J. Clin. Pharmacol. (1987) **27** 1005-1008.

29. Lanoiselee J., Zufferey P.J., Ollier E., Hodin S., Delavenne X., PeriOpeRative Tranexamic acid in hip arthrOplasty study i. Is tranexamic acid exposure related to blood loss in hip arthroplasty? A pharmacokinetic-pharmacodynamic study. Br. J. Clin. Pharmacol. (2018) **84** 310-319.

30. Yang Q.J., Jerath A., Bies R.R., Wasowicz M., Pang K.S. Pharmacokinetic modeling of tranexamic acid for patients undergoing cardiac surgery with normal renal function and model simulations for patients with renal impairment. Biopharm. Drug Dispos. (2015) **36** 294-307.

31. Sharma V., Fan J., Jerath A., Pang K.S., Bojko B., Pawliszyn J. et al. Pharmacokinetics of tranexamic acid in patients undergoing cardiac surgery with use of cardiopulmonary bypass. Anaesthesia. (2012) **67** 1242-1250.

32. Laporte-Simitsidis S., Girard P., Mismetti P., Chabaud S., Decousus H., Boissel J.P. Inter-study variability in population pharmacokinetic meta-analysis: when and how to estimate it? J. Pharm. Sci. (2000) **89** 155-167.

TABLES

Table 1: study information

Study	Publication year	Number of participants	Individual data available	Route	Dose (mg)	Bodyweight (kg)	Age (yrs)	M/F (n)
Chang (22)	2004	12	No	oral	500	Unknown	Unknown	Unknown
Eriksson (23)	1974	2	Yes	IV	1000	69 - 67	29 - 37	2/0
Moore (study 1) (24)*	2012	32	No	oral	1300	62.4 ± 6.7	33 ± 9	0/32
Moore (study 2) (24)*	2012	40	No	oral	1300 x 3 for 5 days	64.4 ± 7.3	33 ± 7	0/40
Pilbrant (25)	1981	3	Yes	IV	1000	66 – 80 – 73	39 – 43 – 36	3/0
Pilbrant (25)	1981	10	Yes	oral	2000	Unknown	Unknown	10/0
Puigdellivol (26)	1985	3	Yes	IV and IM	500	Unknown	23 – 25 – 33	3/0
Sano (27)	1976	3	Yes	IV and IM	1000 - 500	65 – 75 – 76.5	39 – 48 – 51	3/0
Sano (27)	1976	10	Yes	oral	250 - 500	49 to 67	24 to 48	10/0
Sindet-Pedersen (28)#	1987	10	Yes	oral	1000	54 to 90	23 to 29	5/5

Only data with the immediate release formulation* or related to oral route# were used. Individual values are reported when available, otherwise the mean ± SD is reported. Same studies where different administration routes or regimen were used appear in separate lines (24, 25, 27).

Table 2: Parameter estimates of the final tranexamic acid population model.

Parameter	Covariate effect	Estimate (% RSE)	BSV (% RSE)
F_{IM} (%)	-	105 (4.5)	NA
F_{PO} (%)	-	46 (7.9)	0.24 (23)
ka_{IM} (h^{-1})	-	2.24 (28)	0.62 (38)
ka_{PO} (h^{-1})	-	0.279 (10)	0.23 (36)
CL ($L.h^{-1}.70\ kg^{-1}$)	$(BW/70)^{0.75}$	7.6 (4.8)	0.13 (23)
Vc ($L.70\ kg^{-1}$)	$(BW/70)^{1}$	17.9 (5.7)	0.12 (43)
Q ($L.h^{-1}.70\ kg^{-1}$)	$(BW/70)^{0.75}$	2.5 (14)	NA
Vp ($L.70\ kg^{-1}$)	$(BW/70)^{1}$	16.6 (8.6)	NA
Residual var., prop.:			
- Chang *et al.*	NA	0.25 (25)	NA
- Eriksson *et al.*	NA	0.20 (17)	NA
- Moore *et al.*	NA	0.39 (11)	NA
- Pilbrant *et al.*	NA	0.32 (5.9)	NA
- Puigdellivol *et al.*	NA	0.19 (11)	NA
- Sano *et al.*	NA	0.20 (11)	NA
- Sindet-Pedersen	NA	0.33 (10)	NA

Parameters are normalized after a 70 kg subject body weight (BW) according to allometric scaling. % RSE, percent relative standard error; BSV, between-subject variability (η); ka_{PO} and ka_{IM}, oral and intramuscular absorption constants; F_{PO} and F_{IM}, oral and intramuscular bioavailabilities; CL and Q, elimination and inter-compartmental clearances; Vc and Vp, central and peripheral volumes of distribution; NA, not applicable.

FIGURE LEGENDS

Figure 1: **PRISMA flow diagram of study selection.**

Figure 2: Individual pharmacokinetic time-courses of tranexamic acid for 8 representative participants after oral, intramuscular or intravenous administration: blue dots, observations; green line, mean population prediction; purple line, individual predictions.

Figure 3: Diagnostic plots for the final population pharmacokinetic model: representative observed *vs* population- or individual predicted concentrations for two studies with IV, IM and/or oral administrations (25, 27). Blue dots, observations; solid black line, identity line; solid yellow curve, spline; dotted lines, 90% prediction interval.

Figure 4: **Diagnostic plots for the final population pharmacokinetic model:** representative prediction-corrected visual predictive check for one study with oral and IV administration (25). Blue dots depict measured tranexamic acid concentrations; the solid centre lines and the shaded areas stand for the median of observations and the 95% confidence interval of the predictions in the time intervals.

Figure 5: Simulated tranexamic acid concentrations: concentrations predicted in healthy volunteers (upper graphs) or trauma patients (lower graphs) for the different administration routes were simulated for a 70-kg individual after a 1g parenteral or 2g oral dose. Pharmacokinetic parameters of the present study were used for healthy volunteers whereas clearance and volume parameters from a previous study (12) were used for trauma patients, except

absorption parameters, also from the present study. The red line represents the mean and the light blue areas the 95% confidence interval.

Figure 1

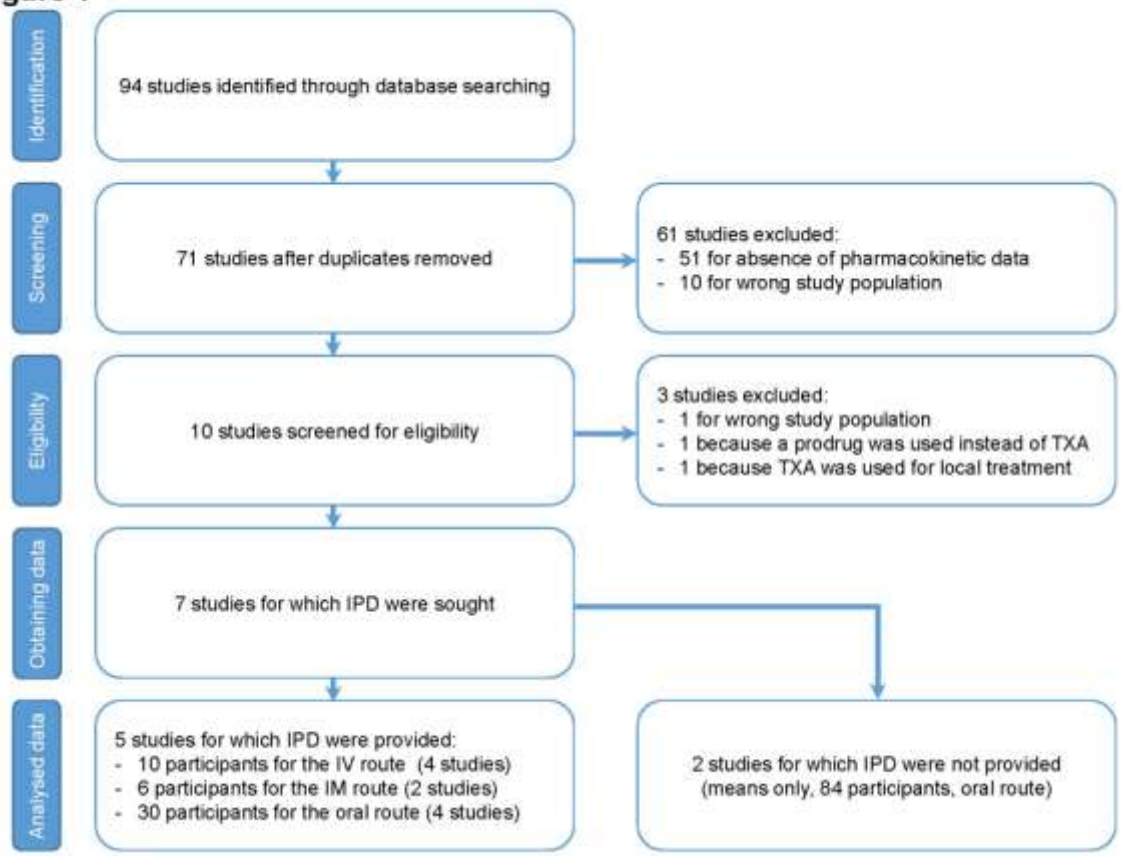

Figure 2

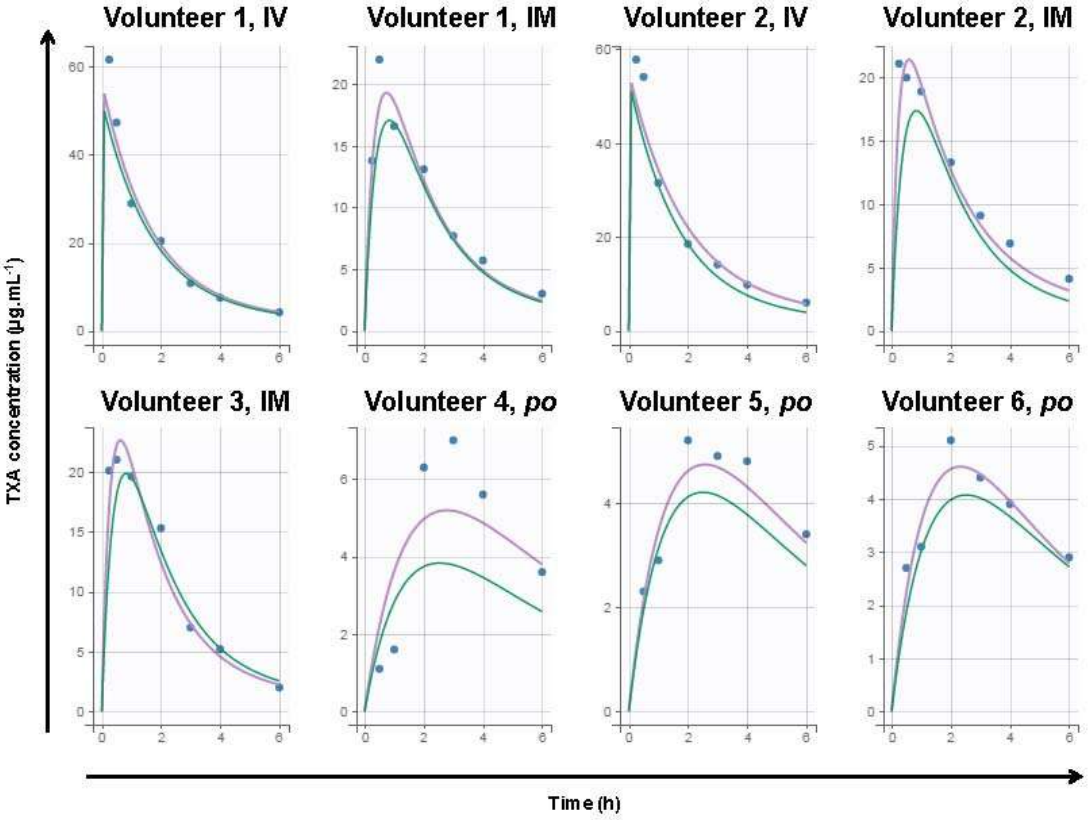

Figure 3

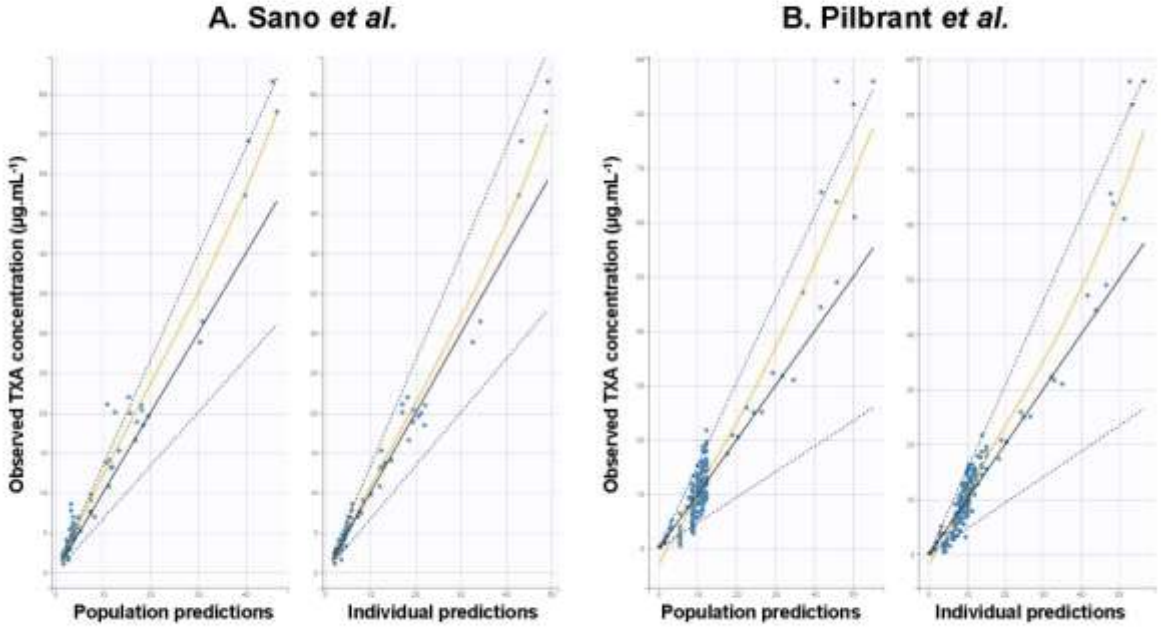

Figure 4

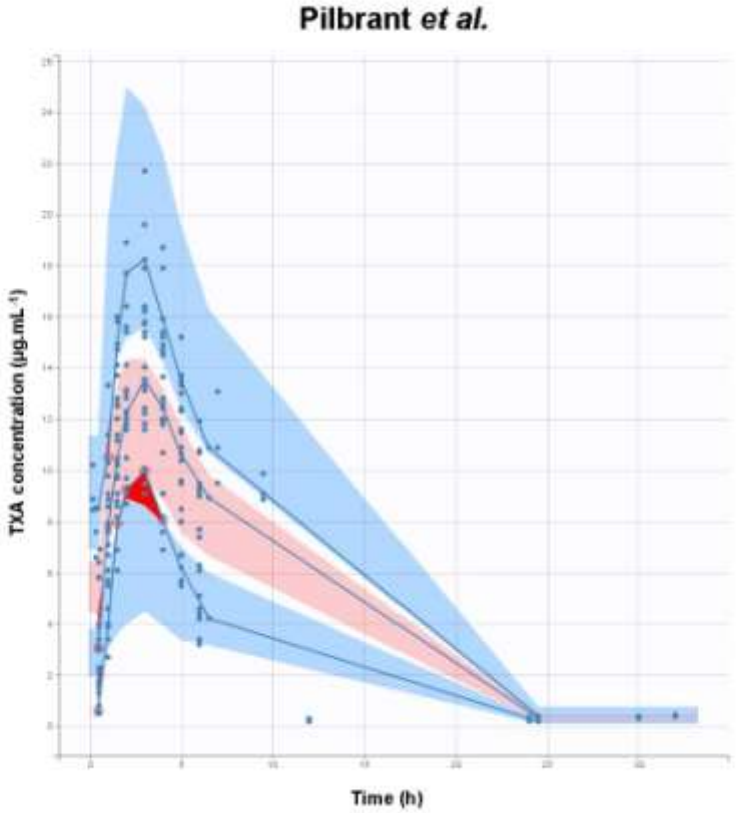

Figure 5