J Vet Intern Med 2013;27:1589–1595

Therapeutic Plasma Concentrations of Epsilon Aminocaproic Acid and Tranexamic Acid in Horses

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Background: Antifibrinolytic drugs such as epsilon aminocaproic acid (EACA) and tranexamic acid (TEA) are used to treat various bleeding disorders in horses. Although horses are hypofibrinolytic compared to humans, dosing schemes have been derived from pharmacokinetic studies targeting plasma concentrations in humans.

Hypothesis/Objectives: We hypothesized therapeutic plasma concentrations of antifibrinolytic drugs in horses would be significantly lower than in humans. Our objective was to use thromboleastography (TEG) and an in vitro model of hyperfibrinolysis to predict therapeutic concentrations of EACA and TEA in horses and humans.

Animals: Citrated plasma collected from 24 random source clinically healthy research horses. Commercial pooled human citrated plasma with normal coagulation parameters was purchased.

Methods: Minimum tissue plasminogen activator (tPA) concentration to induce complete fibrinolysis within 10 minutes was determined using serial dilutions of tPA in equine plasma. Results used to create an in vitro hyperfibrinolysis model with equine and human citrated plasma, and the minimum concentrations of EACA and TEA required to completely inhibit fibrinolysis for 30 minutes (estimated therapeutic concentrations) determined using serial dilutions of the drugs.

Results: Estimated therapeutic concentrations of EACA and TEA were significantly lower in horses (5.82; 95% CI 3.77–7.86 μg/mL and 0.512; 95% CI 0.277–0.748 μg/mL) than in humans (113.2; 95% CI 95.8–130.6 μg/mL and 11.4; 95% CI 8.62–14.1 μg/mL).

Conclusions and Clinical Importance: Current dosing schemes for EACA and TEA in horses may be as much as 20× higher than necessary, potentially increasing cost of treatment and risk of adverse effects.

Key words: Antifibrinolytics; Bleeding disorders; Coagulation; Fibrinolysis.

Antifibrinolytic drugs prevent and stop hemorrhage by inhibiting the breakdown of clots after they have formed. There are 2 categories of antifibrinolytic drugs, lysine analogs (ε-aminocaproic acid [EACA] and tranexamic acid [TEA]) and serine protease inhibitors (aprotinin). Lysine analogs inhibit plasminogen activator, decreasing plasmin formation, and stimulate release of α2-antiplasmin from endothelial cells. Aprotinin directly inhibits plasmin activity.[1]

In human medicine, antifibrinolytics are used primarily in 2 patient populations—trauma victims and surgical patients with or at risk of hemorrhage. In both populations, a shift toward hyperfibrinolysis contributes to premature clot breakdown, bleeding, and coagulopathy, resulting in increased transfusion requirements and mortality.[2,3] A recent large, randomized, placebo-controlled clinical trial showed that human trauma patients treated with TEA had lower overall mortality rates and lower rates of death from bleeding without an increase in thrombotic events.[4] Similarly, several recent meta-analyses and systematic reviews in human medicine have shown significant reductions in blood transfusion requirement and postoperative bleeding complications in adult and pediatric surgical patients without an increased risk of thrombotic or thromboembolic complications.[5–7]

Abbreviations:

CL30′	percent clot lysis at 30 minutes post MA (thromboelastogram)
CLT	clot lysis time (thromboelastogram)
EACA	epsilon aminocaproic acid
HEPES	4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid
MA	maximum amplitude (thromboelastogram)
PAI-1	plasminogen activator inhibitor-1
TEA	tranexamic acid
TEG	thromboelastograph
tPA_{10}	tPA concentration required to obtain a CLT < 10 minutes in horse plasma
tPA	tissue plasminogen activator

EACA has been used most frequently in horses to control bleeding in hemoperitoneum cases.[8,9] Specifically, periparturient mares with hemorrhage from the uterine artery receive EACA routinely, with 92% of mares in a recent study of uterine artery rupture receiving EACA.[10] The effect of EACA in horses with hemoperitoneum has not been well established, but improved outcome is suggested.[8] Current data support the safety of IV infusions EACA in horses and provide thorough information on pharmacokinetics and some data on pharmacodynamics,[11,12] whereas neither the pharmacokinetics or pharmacodynamics of TEA in horses have been studied. Given that both drugs have the same mechanism of action, it is likely that TEA could have utility for the same types of bleeding disorders in horses as EACA, although the authors are

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Submitted April 3, 2013; Revised June 17, 2013; Accepted August 20, 2013.

10.1111/jvim.12202

unaware of any published dosages or reports of TEA use in horses.

Therapeutic plasma concentrations of EACA and TEA have not been determined in horses, and current dosing recommendations for EACA (3.5 mg/kg/min for 15 minutes followed by 0.25 mg/kg/min for the treatment period) target therapeutic plasma concentrations established in humans.[11,13] However, there is evidence that healthy horses may have decreased fibrinolytic activity compared to people, as indicated by lower basal plasminogen activity and increased α-2 antiplasmin and plasminogen activator inhibitor-1 (PAI-1) activity in adult horses and foals.[14–16] In addition, horses require 10-fold higher concentrations of tissue plasminogen activator (tPA) to induce fibrinolysis in an in vitro assay compared to humans.[17] This suggests that EACA and TEA dosing targets based on human data may be excessive in horses. Current dosing regimens for TEA in horses are anecdotal and not supported by pharmacokinetic studies, but dosages of 5–25 mg/kg IV are recommended by one Australian manufacturer for horses.[a]

In humans, an in vitro model of hyperfibrinolysis using pooled human plasma with 1,000 U/mL of tPA added has been used to determine therapeutic concentrations of EACA in adults and neonates using a thromboelastogram (TEG)-based assay.[18] Results were comparable to previous work showing the therapeutic EACA concentration in adults is 130 μg/mL, whereas significantly lower concentrations are needed in neonates (40 μg/mL).[18] Although circulating tPA concentrations in hyperfibrinolytic people (eg, cardiopulmonary bypass patients) are much lower than 1,000 U/mL, local endothelial cell tPA production increases by over 100-fold in hyperfibrinolytic states.[19] This TEG assay has not been used to evaluate effective concentrations of TEA, but studies using other methods suggest 10 μg/mL of TEA is therapeutic in people.[20,21]

The objective of this study was to establish therapeutic plasma concentrations of EACA and TEA in horses by determining plasma concentrations required to reverse an in vitro model of hyperfibrinolysis induced with tPA. We hypothesized that therapeutic plasma concentrations of EACA and TEA for horses would be lower than in humans.

Materials and Methods

The Cornell University and University of Georgia Institutional Animal Care and Use Committees approved blood sample collection for this study. Twenty-four random source horses, deemed healthy based on physical examination were used. Fourteen of the horses were housed at Cornell University and 10 at the University of Georgia, and all were cared for according to the principles outlined in the NIH Guide for the Care and Use of Laboratory Animals. From each horse, 9 mL of blood was collected by jugular venipuncture into a 12 mL polypropylene syringe, containing 1 mL of 3.2% of buffered sodium citrate[b] at a final citrate:blood ratio of 1 : 9. The tubes were centrifuged at 2,500 × *g* for 20 minutes, and 5 mL of citrated platelet-poor plasma from each horse were used to create pooled plasma, which then was stored in aliquots of 5 mL at −80°C until used (within 4 months of collection). Coagulation testing of pooled plasma at 1 laboratory demonstrated that prothrombin time, activated partial thromboplastin time, antithrombin activity, as well as fibrinogen, D-dimer, fibrin degradation product, alpha-2-antiplasmin, and plasminogen concentrations were within the reference interval for each parameter. Commercial pooled human plasma[c] with documented normal coagulation parameters was used for comparison. As per National Institutes of Health guidelines, use of commercially available products for which individual donors cannot be identified does not require institutional approval. For each TEG trial, pooled plasma was thawed in a 37°C water bath and assays were performed within 30 minutes of thawing.

The TEG protocol was a modification of those described by Yurka et al and Nielsen et al.[18,22] Tissue factor-activated TEG was performed in duplicate using the Thrombelastograph Analyzer 5000[d] with standard disposable cups and pins. tPA[e] was reconstituted with sterile water to a final concentration of 1 mg/mL (580,000 units/mL). Tissue factor[f] was reconstituted with sterile water per manufacturer recommendations, and then diluted using HEPES saline with 2% bovine serum albumin to a final dilution of 1 : 1,800 in the TEG cup. Because this study was focused on fibrinolysis, this high concentration of tissue factor was chosen to maximize clot formation and decrease variability in the lysis paramters.[23]

To develop an in vitro model of hyperfibrinolysis, serial dilutions of tPA were added to the plasma sample to achieve the following final tPA concentrations: 100, 200, 300, 400, 500, 550, 600, and 650 U/mL. The clot lysis time (CLT) generated by the TEG software is the time after achieving maximum amplitude (MA) at which the clot strength tracing decreases to <2 mm, corresponding to effective clot dissolution. The goal was to identify the tPA concentration at which CLT was <10 minutes (tPA_{10}), corresponding to an in vitro model in which complete clot dissolution occurred within 10 minutes of maximum clot formation. The tPA concentrations investigated were chosen based on an initial trial and error approach starting at a concentration of 100 U/mL and incrementally increasing the concentration until the tPA_{10} concentration was found. For each assay, 670 μL of plasma, 20 μL of diluted tPA, and 20 μL of diluted tissue factor were mixed in a polypropylene tube by inverting gently 5 times, and 340 μL of the mixture were pipetted into each of 2 cups containing 20 μL of 10% calcium chloride. This allowed all samples to be run in duplicate at 37°C. Tracings were stopped a minimum of 30 minutes after maximum amplitude (MA) was achieved.

Once tPA_{10} was determined for the equine plasma, the in vitro hyperfibrinolysis model consisted of either human or equine plasma with added tPA to reach tPA_{10} as established for the equine plasma. Increasing concentrations of either EACA[g] or TEA[b] were then sequentially added to the reaction mixture until complete inhibition of fibrinolysis at 30 minutes post-MA was observed. Complete inhibition was defined as a TEG CL30′ of 0%. CL30′ was calculated using the equation $100 \times (MA - A30)/MA$, where A30 is the amplitude of the TEG tracing at 30 minutes after MA is reached. This represents the percentage decrease in clot strength 30 minutes after MA. For this part of the experiment, 670 μL of plasma, 10 μL of diluted tPA, 20 μL of diluted tissue factor, and 10 μL of diluted EACA or TEA were mixed in a polypropylene tube by inverting gently 5 times, and 340 μL of the mixture were pipetted into each of 2 cups containing 20 μL of 10% calcium chloride, allowing each assay to be run in duplicate. Samples were run at 37°C. EACA and TEA were diluted with sterile water so that the following final concentrations in the TEG cup were achieved: EACA concentrations in equine plasma were as follows: 1, 2, 3,

3.5, 4.5, 5, 7.5, and 10 μg/mL; EACA concentrations in human plasma were as follows: 30, 50, 62.5, 75, 87.5, 100, 120, and 140 μg/mL; TEA concentrations in equine plasma were as follows: 0.025, 0.05, 0.1, 0.2, 0.3, 0.4, 0.5, and 0.6 μg/mL; and TEA concentrations in human plasma were as follows: 3, 5, 6, 8, 10, and 12 μg/mL. The final EACA and TEA concentrations evaluated in each species were determined by initial exploratory assays to determine the concentrations at which measureable fibrinolysis occurred within 30 minutes and at which fibrinolysis was completely inhibited. Because of previous evidence in the literature suggesting that horses are hypofibrinolytic compared to humans, this exploratory analysis started at lower initial concentrations in the horses (approximately 1/100 the effective concentrations in humans). Serial dilutions between these concentrations then were made to generate dose-response curves for EACA and TEA.

The primary outcome variable examined was the TEG CL30′, allowing comparisons with previous studies investigating adult and neonatal human fibrinolysis. EACA and TEA dose-response curves then were generated, and the CL30′ of fibrinolysis-induced equine and human plasma were compared.

All statistical calculations were performed using commercial software.[h] Linear regression modeling of the CL30′ dose-response curves was used to estimate therapeutic serum concentrations of EACA and TEA for both the equine and human pooled plasma. Because the CL30′ is proportional data and hence the dose-response curve is a sigmoidal shape, an arcsin of the square root transform was applied to linearize the data and stabilize the variance.[24] At the lowest concentrations of antifibrinolytic agents, redundancy in the data was present because of the repeated CL30′ values of 100%. At the highest concentrations, flooring was present because CL30′ values dropped to 0% with complete inhibition of fibrinolysis. Redundancy and flooring of data at the lowest and highest antifibrinolytic agent concentrations were avoided by selecting limited data points in the midrange of concentrations tested that resulted in unique CL30′ values that were <100% and >0%. The relationship between EACA or TEA concentrations and CL30′ was estimated using linear regression analysis, and an inverse prediction point estimation using the slope and intercept from the regression analysis was used to estimate the minimum EACA and TEA concentrations required to achieve a CL30′ of 0% (ie, complete inhibition of fibrinolysis at 30 minutes post-MA). Ninety-five percent confidence intervals for the point estimate also were calculated using this inverse prediction method.[25] Analysis of covariance was used to identify differences between the human and equine concentration-effect curves for both EACA and TEA.

Results

The TEG tracings from the tPA dose-response analysis in pooled equine plasma are shown in Figure 1. A progressive increase in fibrinolysis was noted with increasing tPA concentrations. A tPA concentration of 650 U/mL was required to achieve a CLT of <10 minutes. Therefore, a concentration of 650 U/mL of tPA was used to induce hyperfibrinolysis in all subsequent equine and human plasma assays for the determination of therapeutic concentrations of the antifibrinolytic agents. The CLT of the pooled human plasma with 650 U/mL of tPA was 2.1 minutes.

Concentration-effect curves for equine and human plasma for EACA and TEA are shown in Figures 2 and 3, respectively. The equine curves are shifted to the left compared to the human curves, with complete inhibition of fibrinolysis occurring in horses at much lower concentrations of both drugs than in people. For both the equine and human plasma, statistically significant linear associations between the arcsin square root transformed CL30′ data and antifibrinolytic drug concentrations were identified (all $P < .001$). The estimated minimum effective plasma concentrations of EACA and TEA as well as the 95% confidence intervals for horses and for humans based on the inverse prediction method are summarized in Table 1. For both EACA and TEA, the minimum effective concentrations in equine plasma were approximately 1/20 of those for human plasma. Statistically significant differences between the human and equine concentration-effect curves for both EACA ($P = .012$) and TEA ($P = .005$), with nonoverlapping 95% confidence intervals, were found by analysis of covariance.

Discussion

The plasma concentrations of EACA and TEA in pooled equine plasma required to inhibit fibrinolysis at 30 minutes post-MA in this in vitro model of hyperfibrinolysis (5.82 μg/mL and 0.512 μg/mL, respectively) were approximately 1/20 those required to inhibit fibrinolysis in pooled human plasma (113.2 μg/mL and 11.4 μg/mL, respectively). In addition, the concentrations of EACA and TEA required to inhibit fibrinolysis in this model using pooled human plasma were very similar to previously reported therapeutic concentrations in adult human plasma (130 μg/mL and 10 μg/mL, respectively).[20] This suggests that current dosing schemes for antifibrinolytic agents in horses may be substantially higher than necessary, potentially putting equine patients at risk of thrombotic events or other complications in addition to increasing the cost of treatment.

The concentration of tPA (650 U/mL) used in this study was chosen to facilitate complete in vitro fibrinolysis within 10 minutes of MA in pooled equine plasma. This concentration is much higher than reported circulating concentrations of tPA in healthy horses (1.3–17.6 ng/L or 0.75–10.2 U/mL).[16] However, local endothelial cell production of tPA can increase over 100-fold in hyperfibrinolytic conditions in people,[19] suggesting that similar high concentrations of tPA may be present locally in areas of clot formation. Because such a high concentration of tPA was used in this model system, the differences in response to EACA and TEA between horses and humans in this study are unlikely the result of differences in endogenous tPA concentrations in the pooled plasma from the 2 species. Compared to humans, horses have decreased plasminogen activity (66.5–98.1% versus 80–120%) and increased alpha-2 antiplasmin activity (154–240% versus 70–130%) and PAI-1 concentrations (28.2–33.6 U/mL versus <10 U/mL).[14–16] This combination of decreased profibrinolytic mediators and increased antifibrinolytic mediators could explain the decreased concentrations of EACA and TEA required

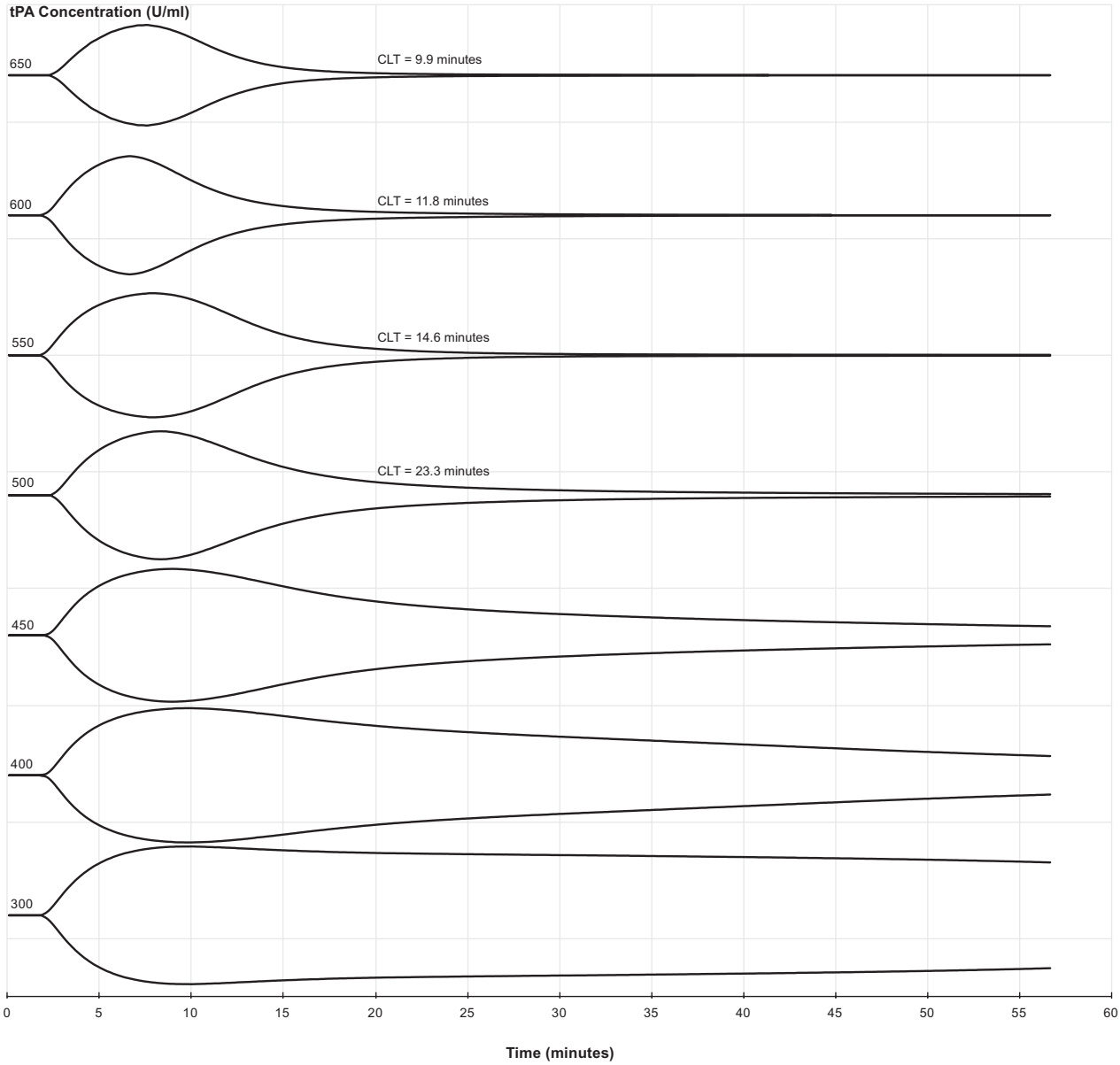

Fig 1. tPA dose-response curves for pooled equine plasma from 24 horses. CLT = clot lysis time, the number of minutes after MA for TEG amplitude to decrease to <2 mm, corresponding to complete clot lysis. At tPA concentrations <500 U/mL, CLT was not achieved within 60 minutes.

to inhibit fibrinolysis in equine plasma in comparison to human plasma noted in this study.

The incidence of hyperfibrinolytic disorders in horses is unknown, and future work targeted at documenting conditions leading to hyperfibrinolysis is warranted. Generally, the evidence suggests that inflammatory diseases in horses are most commonly associated with hypofibrinolysis as assessed by various profibrinolytic and antifibrinolytic biomarkers.[26–28] A recent study using TEG assays to evaluate fibrinolysis more globally also has shown hypofibrinolysis in horses with inflammatory disease.[29] However, another TEG-based study in horses showed that under some conditions, inflammatory disease also may lead to a hyperfibrinolytic state because of a nitric oxide-induced metheme state.[17] Therefore, the use of antifibrinolytic agents in horses with inflammatory disease should be undertaken with caution, and methods to document global hyperfibrinolysis, potentially based upon the TEG assays used in this study, are needed to guide the treatment in horses with inflammatory disease. The contribution of hyperfibrinolytic states to bleeding in horses with hemorrhagic diseases such as hemoperitoneum and traumatic bleeding has not been well-studied, although antifibrinolytic agents are most commonly used in these diseases.[8,10] Future studies aimed at documenting hyperfibrinolysis in hemorrhagic diseases in horses as a rationale for the use of antifibrinolytic

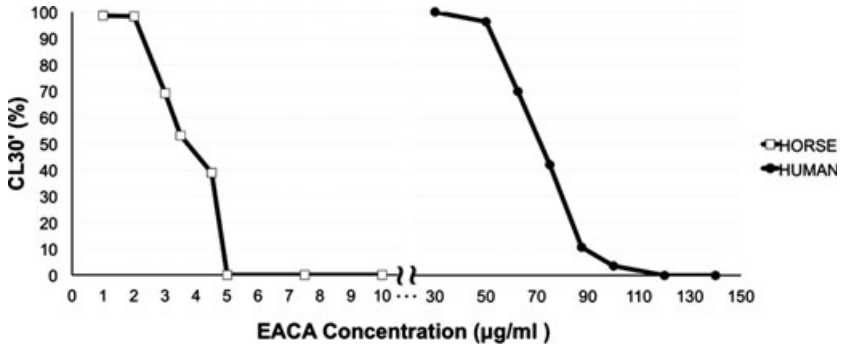

Fig 2. Concentration-effect curves for epsilon aminocaproic acid (EACA) in pooled equine plasma from 24 horses (open squares) and commercial pooled human plasma from at least 30 donors (black circles). Each data point represents the mean of the 2 duplicate assays. CL30′ is the percentage decrease in clot strength 30 minutes after TEG MA, with 100% corresponding to complete lysis and 0% corresponding to absence of lysis.

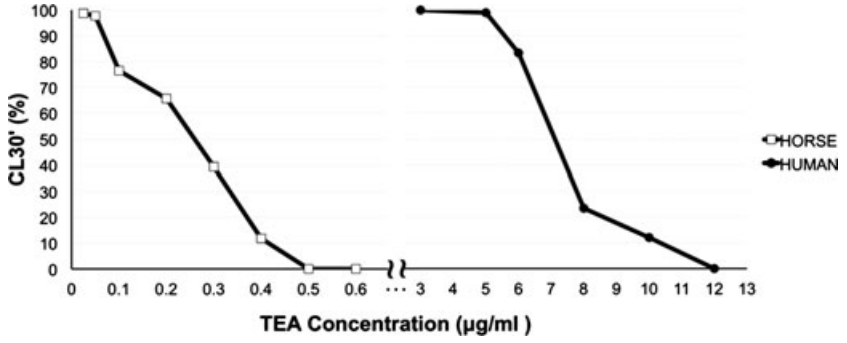

Fig 3. Concentration-effect curves for tranexamic acid (TEA) in pooled equine plasma from 24 horses (open squares) and pooled human plasma from at least 30 donors (black circles). Each data point represents the mean of the 2 duplicate assays. CL30′ is the percentage decrease in clot strength 30 minutes after TEG MA, with 100% corresponding to complete lysis and 0% corresponding to absence of lysis.

Table 1. Estimated therapeutic concentrations of antifibrinolytic drugs in humans and horses.

Species	Estimate (µg/mL)	95% CI (µg/mL)
Epsilon aminocaproic acid (EACA)		
Human	113.2	95.8–130.6
Horse	5.82	3.77–7.86
Tranexamic acid (TEA)		
Human	11.4	8.62–14.1
Horse	0.512	0.277–0.748

agents is warranted. Even in the absence of measureable systemic hyperfibrinolysis, agents that enhance clot strength and viability still may be clinically valuable. Ultimately, prospective, randomized, placebo-controlled clinical trials investigating the utility of these drugs in bleeding horses are needed.

We did not establish a specific tPA_{10} for the pooled human plasma, and instead used the same tPA concentration for the pooled human plasma as for the pooled equine plasma to keep the models as consistent as possible between the species. The CLT of the pooled human plasma with 650 U/mL of tPA added was 2.1 minutes, shorter than the 10 minutes of the pooled equine plasma. This may have effectively led to a more severely hyperfibrinolytic human plasma model than horse plasma model. However, the therapeutic plasma concentrations of EACA and TEA estimated by this model were very similar to previously published reports in humans, including those derived using 1,000 U/mL of tPA, providing some evidence of the validity of this model in human plasma.

This study has several limitations. Because it is an in vitro model, the local effects of endothelial cells on fibrinolysis were not reproduced, limiting our ability to fully assess the fibrinolytic potential of horses. In addition, because the model used pooled, platelet-poor plasma, the influence of blood cells (platelets, leukocytes, and erythrocytes) could not be evaluated. Antifibrinolytic drugs are used in ill animals at risk of bleeding that are receiving other drugs that could affect fibrinolysis, but these assays were carried out using pooled plasma from healthy horses, making it impossible to determine the effects of concurrent drug therapy and the underlying disease states on hemostasis. Therefore, until additional

studies in sick horses are available, extrapolation of these therapeutic concentrations to sick horses should be performed cautiously. However, current dosing schemes of antifibrinolytic agents in humans and horses are based on in vitro data using healthy human donors, including those after which this study was modeled.[18,22]

In conclusion, this in vitro model of hyperfibrinolysis using pooled plasma from healthy subjects showed that the minimum concentrations of EACA and TEA required to inhibit fibrinolysis in horses were approximately 1/20 those required in humans. Current dosing schemes for these drugs in horses, which are based on therapeutic concentrations in people, may result in substantial overdosing, increasing the expense of treatment and the potential for complications such as thrombosis. Future in vivo studies aimed at confirming these findings are warranted.

Footnotes

[a] Ilium Vasolamin S 100; Troy Laboratories, Glendenning, NSW, Australia
[b] Sigma-Aldrich Corporation, Saint Louis, MO
[c] FACT; George King Biomedical, Overland Park, KS
[d] Haemoscope, Skokie, IL
[e] Alteplase; Genentech, South San Francisco, CA
[f] Dade Innovin; Siemens Healthcare Diagnostics Inc, Newark, DE
[g] Aminocaproic acid for injection, Hospira, Inc, Lake Forest, IL
[h] MedCalc for Windows, version 9.5.0.0; MedCalc Software, Mariakerke, Belgium

Acknowledgments

Grant support: Funding was provided by the University of Georgia Equine Programs "For the Love of the Horse Program".

Conflict of Interest Declaration: Authors disclose no conflict of interest.

References

1. Ray MJ, Hales M, Marsh N. Epsilon-aminocaproic acid promotes the release of alpha2-antiplasmin during and after cardiopulmonary bypass. Blood Coagul Fibrinolysis 2001;12:129–35.

2. Levy JH, Dutton RP, Hemphill JC, et al. Multidisciplinary approach to the challenge of hemostasis. Anesth Analg 2010;110:354–64.

3. Ives C, Inaba K, Branco BC, et al. Hyperfibrinolysis elicited via thromboelastography predicts mortality in trauma. J Am Coll Surg 2012;215:496–502.

4. CRASH-2 Trial Collaborators. 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.

5. Sukeik M, Alshryda S, Haddad FS, et al. Systematic review and meta-analysis of the use of tranexamic acid in total hip replacement. J Bone Joint Surg Br 2011;93:39–46.

6. Henry DA, Moxey AJ, Carless PA, et al. Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion. Cochrane Database Syst Rev 2011;(1):CD001886.

7. Schouten ES, van de Pol AC, Schouten ANJ, et al. The effect of aprotinin, tranexamic acid, and aminocaproic acid on blood loss and use of blood products in major pediatric surgery: A meta-analysis. Pediatr Crit Care Med 2009;10:182–90.

8. Dechant JE, Nieto JE, Le Jeune SS. Hemoperitoneum in horses: 67 cases (1989-2004). J Am Vet Med Assoc 2006;229:253–8.

9. Conwell RC, Hillyer MH, Mair TS, et al. Haemoperitoneum in horses: A retrospective review of 54 cases. Vet Rec 2010;167:514–8.

10. Arnold CE, Payne M. Thompson J a, et al. Periparturient hemorrhage in mares: 73 cases (1998-2005). J Am Vet Med Assoc 2008;232:1345–51.

11. Ross J, Dallap BL. Dolente B a, et al. Pharmacokinetics and pharmacodynamics of epsilon-aminocaproic acid in horses. Am J Vet Res 2007;68:1016–21.

12. Heidmann P, Tornquist SJS, Qu A, et al. Laboratory measures of hemostasis and fibrinolysis after intravenous administration of ε-aminocaproic acid in clinically normal horses and ponies. Am J Vet Res 2005;66:313–318.

13. Frederiksen MC, Bowsher DJ, Ruo TI, et al. Kinetics of epsilon-aminocaproic acid distribution, elimination, and antifibrinolytic effects in normal subjects. Clin Pharmacol Ther 1984;35:387–93.

14. Tentoni J, Polini N, Casanave E. Comparative vertebrate fibrinolysis. Comp Clin Pathol 2010;19:225–234.

15. Barton M, Morris D. Hemostatic and fibrinolytic indices in neonatal foals with presumed septicemia. J Vet Intern Med 1998;12:26–35.

16. Keen J, Mclaren M, Chandler K, et al. Biochemical indices of vascular function, glucose metabolism and oxidative stress in horses with equine Cushing's disease. Equine Vet J 2010;36:226–229.

17. Olver CS, Nielsen VG. Thrombelastographic characterization of coagulation/fibrinolysis in horses: Role of carboxyheme and metheme states. Blood Coagul Fibrinolysis 2012;23:231–6.

18. Yurka HG, Wissler RN, Zanghi CN, et al. The effective concentration of epsilon-aminocaproic acid for inhibition of fibrinolysis in neonatal plasma in vitro. Anesth Analg 2010;111:180–4.

19. Hrafnkelsdottir T, Gudnason T, Wall U, et al. Regulation of local availability of active tissue-type plasminogen activator in vivo in man. J Thromb Haemost 2004;2:1960–8.

20. Verstraete M. Clinical application of inhibitors of fibrinolysis. Drugs 1985;29:236–61.

21. Andersson L, Nilsoon IM, Colleen S, et al. Role of urokinase and tissue activator in sustaining bleeding and the management thereof with EACA and AMCA. Ann N Y Acad Sci 1968;146:642–58.

22. Nielsen VG, Cankovic L, Steenwyk BL. Epsilon-aminocaproic acid inhibition of fibrinolysis in vitro: Should the "therapeutic" concentration be reconsidered? Blood Coagul Fibrinolysis 2007;18:35–9.

23. Smith SA, McMichael M, Galligan A, et al. Clot formation in canine whole blood as measured by rotational thromboelastometry is influenced by sample handling and coagulation activator. Blood Coagul Fibrinolysis 2010;21:692–702.

24. Sokal R, Rohlf J. Biometry, the Principles and Practice of Statistics in Biological Research, 2nd ed. San Francisco, CA: W. H. Freeman & Company; 1981.

25. Neter J, Kutner M, Wasserman W, et al. Applied Linear Regression Models. New York, NY: McGraw-Hill/Irwin; 1994.

26. Collatos C, Barton MH, Moore JN. Fibrinolytic activity in plasma from horses with gastrointestinal diseases: Changes

associated with diagnosis, surgery, and outcome. J Vet Intern Med 1995;9:18–23.

27. Collatos C, Barton MH, Prasse KW, et al. Intravascular and peritoneal coagulation and fibrinolysis in horses with acute gastrointestinal tract diseases. J Am Vet Med Assoc 1995;207:465–70.

28. Welles EG, Prasse KW, Moore JN. Use of newly developed assays for protein C and plasminogen in horses with signs of colic. Am J Vet Res 1991;52:345–51.

29. Epstein K, Brainard B, Gomez-Ibanez M, et al. Thrombelastography in horses with acute gastrointestinal disease. J Vet Intern Med 2011;25:307–314.