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Original Contribution

Comparison of tranexamic acid plasma concentrations when administered via intraosseous and intravenous routes☆

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ABSTRACT

Introduction: There is a lack of information regarding intraosseous (IO) administration of tranexamic acid (TXA). Our hypothesis was that a single bolus IO injection of TXA will have a similar pharmacokinetic profile to TXA administered at the same dose IV.
Methods: Sixteen male Landrace cross swine (mean body weight 27.6 ± 2.6 kg) were divided into an IV group (n = 8) and an IO group (n = 8). Each animal received 30 mg/kg TXA via an IV or IO catheter, respectively. Jugular blood samples were collected for pharmacokinetic analysis over a 3 h period. The maximum TXA plasma concentration (C_{max}) and corresponding time as well as distribution half-life, elimination half-life, area under the curve, plasma clearance and volume of distribution were calculated. One- and two-way analysis of variance for repeated measures (time, group) with Tukey's and Bonferonni post hoc tests were used to compare TXA plasma concentrations within and between groups, respectively.
Results: Plasma concentrations of TXA were significantly higher ($p < 0.0001$) in the IV group during the TXA infusion. C_{max} occurred at 4 min after initiation of the bolus in the IV group (9.36 ± 3.20 ng/μl) and at 5 min after initiation of the bolus in the IO group (4.46 ± 0.49 ng/μl). Plasma concentrations were very similar from the completion of injection onwards. There were no significant differences between the two administration routes for any other pharmacokinetic variables measured.
Conclusion: The results of this study support pharmacokinetic bioequivalence of IO and IV administration of TXA.

1. Introduction

Following promising preliminary results from human studies such as the CRASH-2 and MATTERs studies, administration of intravenous (IV) tranexamic acid (TXA), an anti-fibrinolytic agent, is currently included in several civilian and military human trauma and resuscitation protocols [1,2]. Military Damage-Control Resuscitation Clinical Practice Guidelines state that the early use of IV TXA should be strongly considered for any patient requiring blood products in the treatment of combat-related hemorrhage and is most strongly advocated in patients judged likely to require massive transfusion [2,3]. Although these studies suggest that early administration of TXA (≤1 h following trauma) is associated with the greatest decrease in hemorrhage-related deaths, there is also evidence to suggest that its administration ≥3 h after injury may be harmful [1]. The narrow therapeutic timeline for TXA underscores the need to establish effective routes of administration to ensure trauma patients receive TXA in a timely fashion.

Several current guidelines state that if resuscitation is required and IV access is not obtainable, the intraosseous (IO) route should be used for certain medications [3,4]. Given the safety of administration of other medications via the IO route, and the fact that TXA has a pH similar to that of sodium chloride 0.9% solution and blood products [5], the use of IO TXA has been suggested should IV access not be available [4,6]. Despite evidence supporting the IO administration of drugs, there is a paucity of literature regarding the administration of IO TXA as a life-saving option in cases of failed or impossible IV catheterization [7].

The limited use of TXA via the IO route is likely explained by the fact that it has not been established if alternative routes of administration of TXA (i.e., IO, intramuscular, etc.) provide the same benefits that have been prospectively demonstrated with the IV route [5]. This has led to some authors cautioning against the use of IO TXA as equivalency between IO and IV routes has not been established and Pfizer recommends only intravenous administration, for which the detailed pharmacokinetics of TXA have been demonstrated [8]. It is apparent that studies investigating the administration of IO TXA are needed. In fact, on the initiative of the American military, a group of panel experts

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recently identified potential routes of TXA administration (IV, oral, IO, transmucosal) as a Priority 2 research requirement [5].

The objective of this study was to determine if plasma levels of TXA are similar when given IO versus IV. We hypothesised that a single bolus IO injection of TXA will have a similar pharmacokinetic profile to TXA administered at the same dose IV.

2. Methods

This study was approved by the University of Calgary Animal Care Committee (Protocol AC15-0068) and the animals were managed in accordance with the Canadian Council on Animal Care standards.

2.1. Animal Preparation

Sixteen male Landrace-Large White cross swine with a mean body weight of 27.6 ± 2.6 kg were included in the study. The pigs were sourced from a commercial swine production unit, housed individually or in groups of 2 and fed a pelleted swine ration twice daily with ad libitum access to nipple water feeders. Each pig was kept in an individual pen and fasted with ad libitum access to water for twelve hours before premedication.

2.2. Anesthesia

Swine were premedicated with intramuscular (IM) azaperone 6 mg (Stresnil 40 mg/ml, Vétoquinol Inc., Lavaltrie, QC, Canada J5 T 3S5), dexmedetomidine 0.6 mg (Dexdomitor 0.5 mg/ml, Zoetis Inc., Kalamazoo, MI, USA 49007) and alfaxalone 60 mg (Alfaxan 10 mg/ml, Jurox Pty Ltd., Rutherford, NSW, Australia 2320). Swine were weighed prior to induction of anesthesia. A 22 gauge (G), two-port catheter (BD Saf-T-Intima IV Catheter, Becton Dickinson, Sandy, UT, USA 84070) was placed in an auricular vein of both ears and induction was completed with 1–2 mg/kg IV alfaxalone, titrated to effect. Animals receiving IV TXA had one ear marked 'TXA' in permanent ink to ensure that that particular auricular catheter was dedicated to the TXA bolus only.

Anesthesia was delivered using a circle system with isoflurane (F_I'Iso 1.3–2%) and oxygen ($F_I'O_2$ 100%). Two constant rate infusions (alfaxalone 25 μg/kg/min and dexmedetomidine 2 μg/kg/h) were administered via one of the auricular catheters using digitally programmable syringe drivers (Medfusion 3500, Smiths Medical International, St. Paul, MN, USA 55112). A 7.5 ml/kg/h continuous rate infusion (CRI) of 0.9% saline (1000 ml 0.9% Sodium Chloride, Baxter Corp, Mississauga ON, Canada L4Z 3Y4) was administered for the duration of the experiment into the TXA-designated auricular catheter to maintain patency.

2.3. Instrumentation

Instrumentation included a 5-lead electrocardiogram (ECG), buccal pulse oximeter, sidestream capnograph, spirometer, tissue oxygen saturation monitor, bispectral index (BIS) and a rectal thermometer. The ECG, pulse oximeter, capnograph and spirometry data were displayed and recorded with a multiparameter monitor (Datex-Ohmeda s/5 Collect, GE Healthcare, Helsinki, Finland FIN-00031). The BIS electrodes (BIS Pediatric™ Sensor, Covidien LLC, 15 Hampshire Street, Mansfield, MA, U.S.A. 02 048) were placed horizontally across a clipped area of skin overlying the frontal bone and right lateral aspect of the skull and connected to a BIS monitor (BIS Vista Monitoring System, Aspect Medical Systems, Norwood, MA, USA 02062). Animals were placed into dorsal recumbency for the duration of the study.

One common carotid artery was catheterized to perform intermittent arterial blood gas analysis and continuous arterial blood pressure monitoring (systolic, diastolic and mean). An external jugular vein was also catheterized to allow TXA blood sampling. A tissue saturation sensor (Inspectra StO_2 Sensor, model 1615, Hutchinson Technology, 40 West Highland Park Drive NE, Hutchinson, MN, USA 55350) was placed over the right adductor muscle. Rectal body temperature was measured with a pliable rectal probe (Datex-Ohmeda s/5 Collect, GE Healthcare, Helsinki, Finland FIN-00031) and maintained between 37 and 38 °C using a circulating water pad as needed.

The IO TXA animals received an IO catheter (Arrow EZ-IO®, pediatric, pink 15 G × 15 mm, Teleflex Incorporated, Wayne, PA) that was inserted by a single experienced operator into the right proximal tibia just medial to the tibial tuberosity. A power drill (Arrow EZ-IO®, Power Driver – G3, Teleflex Incorporated, Wayne, PA) was used and a 90° angle to the bone surface was maintained during insertion. The stylet was removed, blood was observed back-flowing through the hub, and an extension set was attached (EZ® Connect, Teleflex Incorporated, Wayne, PA). A small amount of blood was aspirated and the catheter was flushed with 20 ml heparinized saline to ensure patency.

2.4. Experimental Design

Sixteen animals were used in the study and all were included in the data analysis. Animals were divided into two groups. Each pig in the IV group (n = 8) received 30 mg/kg of IV TXA (Tranexamic Acid 100 mg/ml, Sandoz, QC, Canada, J4B 7 K8), followed by a 1 ml/kg saline bolus. Each pig in the IO group (n = 8) received 30 mg/kg TXA via the IO catheter followed by a 1 ml/kg saline bolus. The TXA dose was made up to a total of 25 ml using saline as the diluent in both groups and the solution was administered over 5 min using a digitally programmable syringe driver. The saline bolus was manually administered over 1 min.

None of the observers were blinded to treatment. The experimental protocol was divided into 2 phases. A detailed data collection timeline is shown in Table 1. The first 30 min established anesthetic and physiologic equilibration prior to the second phase. During the second phase physiologic recording and blood sampling were conducted. Data including heart rate, ECG, direct arterial blood pressure, end tidal CO_2, BIS, tissue oxygen saturation, respiratory rate, tidal volume, minute volume, and rectal temperature were collected continuously. Arterial blood

Table 1
Timeline for pharmacokinetic, arterial blood gas, and physiologic data collection prior to and following intraosseous (IO, n = 8) and intravenous (IV, n = 8) tranexamic acid (TXA) administration of 30 mg/kg over 5 min and a total jugular venous sampling period of 3 h. Intravenous injection was via an auricular vein and IO infusions were through the right proximal tibia.

Time point	Description	Data collected
SSA	Steady state anesthesia	pK, ABG, PP
Baseline (BL)	Immediately before TXA bolus	pK, ABG, PP
Ti	TXA bolus 1 min	pK, PP
Tii	TXA bolus 2 min	pK, PP
Tiii	TXA bolus 3 min	pK, PP
Tiv	TXA bolus 4 min	pK, PP
Tv	TXA bolus 5 min	pK, ABG, PP
T1	Post TXA bolus + 1 min, end saline bolus	pK, PP
T2	Post TXA bolus + 2 min	pK, PP
T4	Post TXA bolus + 4 min	pK, PP
T6	Post TXA bolus + 6 min	pK, PP
T8	Post TXA bolus + 8 min	pK, PP
T10	Post TXA bolus + 10 min	pK, ABG, PP
T15	Post TXA bolus + 15 min	pK, ABG, MVBG, PP
T20	Post TXA bolus + 20 min	pK, ABG, PP
T25	Post TXA bolus + 25 min	pK, ABG, PP
T30	Post TXA bolus + 30 min	pK, PP
T45	Post TXA bolus + 45 min	pK, ABG, MVBG, PP
T60	Post TXA bolus + 60 min	pK, ABG, PP
T80	Post TXA bolus + 80 min	pK, ABG, PP
T100	Post TXA bolus + 100 min	pK, ABG, PP
T120	Post TXA bolus + 120 min	pK, ABG, PP
T150	Post TXA bolus + 150 min	pK, ABG, PP
T180	Post TXA bolus + 180 min	pK, ABG, PP

PP: physiologic parameters including cardiac and respiratory values, tissue oxygen saturation, rectal body temperature, and bispectral index data were collected continuously; pK: jugular venous sample for pharmacokinetic analysis; ABG: arterial blood gas; MVBG: mixed venous blood gas.