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Intramuscular tranexamic acid: a real-world application of pharmacokinetics

Andrea Cortegiani[1,2,*], Anthony R. Absalom[3] and Beverley J. Hunt[4]

[1]Department of Surgical Oncological and Oral Science (Di.Chir.On.S), University of Palermo, Palermo, Italy, [2]Department of Anaesthesiology Intensive Care and Emergency, Policlinico Paolo Giaccone, Palermo, Italy, [3]University Medical Center Groningen, University of Groningen, Groningen, the Netherlands and [4]Kings Healthcare Partners, Thrombosis & Haemophilia Centre, Guy's & St Thomas' NHS Foundation Trust, London, UK

*Corresponding author. E-mail: andrea.cortegiani@unipa.it

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For many anaesthetists around the world, the mere mention of the word 'pharmacokinetics' is sufficient to make their eyes glaze over and their attention wander. Pharmacokinetics is seen as an art that is as obscure and esoteric as the art of divination (prediction) practiced by the likes of Professor Sybille Trelawny[1] but that has varying and mostly limited relevance to clinical practice. Although this hyperbole may have elements of truth, it is a fact that pharmacokinetic data are the essential foundation upon which rational drug dosing guidelines are developed for all drugs.

Such data underpin the dosing guidelines for oral and intravenous administration of tranexamic acid (TXA), a cheap and widely available plasmin inhibitor.[2] TXA is a synthetic analogue of the amino acid lysine that was developed in the 1950s in Japan by Utako and Shosuke Okamoto. It is a competitive inhibitor of plasmin, which binds to lysyl residues, so the antifibrinolytic effect is the result of inhibition of the interaction between plasmin and the lysyl binding sites of fibrin.

The global burden of death from trauma is staggering (close to 5 million deaths per annum), and many who survive are disabled and unable to work.[3,4] In 2016 homicides resulted in half a million deaths and suicides in 800 000 deaths, whereas road traffic injuries resulted in 1.35 million deaths.[5] Low-income countries are particularly hard hit by road traffic injuries, with an annual death rate of 27.5 per 100 000, compared with only 8.3 per 100 000 in high-income countries. Overall, >90% of global trauma deaths occur in low- and middle-income countries.[6] About 24% of trauma-related deaths are directly or indirectly caused by haemorrhage.[7]

The Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage-2 (CRASH-2) trial showed that in 20 211 trauma patients with a significant risk of bleeding, TXA 1 g i.v. followed by another 1 g over 8 reduced the risk of death caused by bleeding from 5.7% to 4.9% (relative risk=0.85; 95% confidence interval [CI], 0.76–0.96; P=0.0077).[8] Most national and international guidelines including the European guidelines on major bleeding and coagulopathy after trauma made TXA administration a Grade 1 recommendation in adult trauma patients who are bleeding or at risk of haemorrhage within 3 h of the event, considering the body of evidence on effectiveness and safety.[7,9]

Postpartum haemorrhage is another major global health problem. It receives little media attention, even though ~14 million women suffer postpartum haemorrhage every year resulting in significant morbidity and mortality.[10] Although the incidence of postpartum haemorrhage appears to be increasing in high-income countries,[11] the absolute rate is low and death is rare in these countries. The problem resides in low- and middle-income countries which account for 99% of the hundreds of thousands of annual deaths (the true death rate is unknown as, owing to the poor social status of women, their deaths may not be registered).[12] In the World Maternal Antifibrinolytic (WOMAN) trial, intravenous TXA given as a 1 g bolus followed by another 1 g if bleeding continues or restarts reduced deaths caused by bleeding from 1.9% to 1.5% of all woman randomised to receive TXA as opposed to placebo (risk ratio [RR]=0.81; 95% CI, 0.65–1.00; P=0.045; number needed to treat: 250 patients to prevent one death). The benefit was greater in those who received TXA within 3 h of birth (deaths caused by bleeding in 1.2% in the TXA group *vs* 1.7% in the placebo group (RR=0.69; 95% CI, 0.52–0.91; P=0.008).[13] There was no significant effect of TXA on the primary composite outcome (death from all causes or hysterectomy) and on all-cause mortality.[13] In 2017, the WHO recommended early (within 3 h) intravenous use of TXA for all women with a clinical diagnosis of postpartum haemorrhage.[14] Of note, the WHO also recommended that research on alternative administration routes for TXA should be a major priority.[15]

Before intramuscular administration of any drug can be approved and recommended, sufficient knowledge of the pharmacokinetic properties of that drug after intramuscular administration is required. Although the pharmacokinetics of intramuscular TXA has been described adequately in healthy volunteers,[14,16] until recently there were no available data from patients with significant haemorrhage, in whom resulting pathophysiological changes can significantly alter important pharmacokinetic determinants such as muscle perfusion and hepatic blood flow.

In this issue of the *British Journal of Anaesthesia*, Grassin-Delyle and colleagues[17] remedy this hiatus with publication of the results of a study of intramuscular TXA administration in patients with significant injury and severe bleeding. Thirty adult subjects were included if they had received TXA 1 g i.v., and if a second dose of TXA was indicated. Subjects then received a further 1 g of TXA administered as two intramuscular injections of 0.5 g TXA (5 ml) into uninjured muscles. Blood samples were collected at eight time points, from 10 min after intravenous injection up until 10 h thereafter. These data were then subjected to non-linear mixed-effects modelling. Pharmacokinetic 'wizards' will be reassured by the presence in the article of the necessary simultaneous differential equations, rate constants and other model parameters, and graphics such as diagnostic plots. As with other drugs used in anaesthesia,[18,19] the pharmacokinetics of TXA were best explained by a two-compartment model comprising a central (V_c) and a peripheral compartment (V_p). Absorption from the intramuscular depot into the central compartment was a first-order process (k_a=1.94 h^{-1}) that was not influenced by shock or other variables, with a bioavailability of 77%. Intercompartmental clearance and elimination clearance from the central compartment were also first-order processes. V_c scaled allometrically with age and was ~50% lower in the presence of signs of shock. Clearance and intercompartmental clearance scaled allometrically with body weight.

Whether clinicians are 'muggles' (those not born into the mystical pharmacokinetic world) or 'wizards', they are

however likely to be even more impressed with the implications of these results and of the analyses and simulations. The study has three findings that are important for all practitioners dealing with bleeding patients. Firstly, absorption after intramuscular injection was effective and reasonably rapid (absorption half-life of ~21 min, which is not too different from that of morphine in healthy volunteers [7.7 min[18]]). More importantly, absorption was predictable and not influenced by factors such as clinical status or organ perfusion (e.g. signs of shock, blood lactate), injection site, type of injury, anthropometric variables, and glomerular filtration rate. This predictability of absorption can be seen in Figure 1 of the article. We commend the authors for presenting this figure, which shows the raw data (measured TXA concentrations) for all patients and time points, meaning that no special 'Mirror of Erised'[20] is required to demonstrate the 'desired' findings. Secondly, the results of simulations using the pharmacokinetic parameters obtained from the modelling show that had TXA only been administered intramuscularly, plasma concentrations would have reached therapeutic levels (5–10 mg L^{-1}) within 15 min and would have remained above these levels for several hours. Finally, intramuscular administration of TXA appeared to be safe, as only mild local transient side-effects including erythema, induration, bruising, or subcutaneous nodules were reported (14 out 30 patients). One patient developed pyrexia after 2 days, and there were no serious adverse events.

There are many situations in which the intravenous route is not available for administration of this potentially life-saving medication. In low-income countries, limited infrastructure and inadequate numbers of trained healthcare professionals mean that there can be delays of several hours or even days before intravenous access is secured. Even in medium- and high-income countries there are situations in which intravenous access might be delayed (e.g. isolated/rural areas and the battlefield). In these situations, the intramuscular route can be useful, as it requires little equipment and training, and has been used successfully for administration of drugs such as epinephrine, morphine, ketamine, and naloxone, in some cases by nurses or paramedics, and in other cases by the patient themselves. No big leap is required to train nurses, midwives, paramedics, and even first responders including policemen, soldiers, or firefighters to administer TXA intramuscularly.

We recognise that although the findings presented are impressive and potentially exciting, there are several limitations. Although the study cohort is representative of the trauma population, it was performed in only a single high-income country. Thus, external validation in patients from low- and middle-income countries, and in settings other than trauma (such as postpartum haemorrhage) may be needed to confirm generalisability of the model parameters and predictions in other populations. Secondly, it is important to state the obvious fact that TXA is no 'magic bullet'. Avoiding deaths from trauma or postpartum haemorrhage involves a multifaceted approach, starting with prevention in the case of trauma, and TXA is but one part of this approach, in patients with bleeding.

Finally, this study confirms (if confirmation was needed) that pharmacokinetic studies are able to give answers to important research questions with strong clinical implications. In this case this was an alternative route to administer a potentially life-threatening drug to bleeding patients in low- to middle-income countries. Pharmacokinetic analysis is 'esoteric art' with relevant worldwide clinical potential!

Authors' contributions

All authors contributed substantially to the conception of the content, drafting the article or revising it critically for important intellectual content, read and approved the final version of the manuscript.

Declarations of interest

AC is an editorial fellow for the *British Journal of Anaesthesia*, and received honoraria for lectures from Pfizer (New York, NY, USA) and Thermofisher (Waltham, MA, USA).

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Comparative videolaryngoscope performance in children: data from the Pediatric Difficult Intubation Registry

Andrew Norris[1,*] and James Armstrong[2]

[1]King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia and [2]Nottingham University Hospitals NHS Trust, Nottingham, UK

*Corresponding author. E-mail: andrewnorris@kfshrc.edu.sa

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In 2003, the *British Journal of Anaesthesia* published a paper evaluating a novel device for tracheal intubation in cervical spine disease, the Glidescope.[1] Since then, evidence of the benefits of videolaryngoscopy over conventional direct laryngoscopy has gradually accumulated.[2] Videolaryngoscopy improves various measures related to tracheal intubation when compared with direct laryngoscopy in a wide range of contexts ranging from predicted difficulty, simulated difficulty, and even microgravity.[3] The accumulating evidence of improved success, improved visualisation (with its associated reduction in injury), reduced number of attempts, and even improved learning, has recently led to recommendations for the universal adoption of videoolaryngoscopy.[4] Certainly, the technique was firmly established in many countries even before the novel coronavirus disease 2019 (COVID-19) pandemic.[5] Guidelines on tracheal intubation in COVID-19 patients have included use of videolaryngoscopy, which allows clinicians to work further away from the open airway, thus reducing their exposure to aerosol and droplet material during tracheal intubation, and anecdotally there has been a significant expansion of videolaryngoscopy use as a result.[6,7] However, the choice between videoscopes remains unclear.

Multiple prospective studies have been conducted comparing different videolaryngoscopes in an attempt to find the 'best' device, often with conflicting results.[8] Generalisable evidence from prospective clinical trials in the area of airway management, including the assessment of devices, is certainly challenging. Such studies are difficult to control for confounding factors, the population of interest is typically small, the required sample size is large, and surrogate outcomes are typically required. These studies therefore require cautious interpretation, as the best choice is likely to be context-sensitive in terms of the patient group, the type of airway difficulty, and the clinician's experience and competence. Even with well-conducted studies with strong internal validity it is difficult to generalise. Meanwhile, the questions of which laryngoscope to use in a specific case or when purchasing

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