

Anaphylaxis to tranexamic acid—a rare reaction to a common drug



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Clinical Implications

- Tranexamic acid is commonly used but hypersensitivity reactions are rare. We propose an algorithm for the investigation of anaphylaxis to this drug that includes suggested concentrations for skin testing, protocol for provocation testing, and recommendations regarding cross-reactive antifibrinolytic agents.

TO THE EDITOR:

Tranexamic acid (TXA) is a widely used antifibrinolytic drug, but allergy to TXA has rarely been reported. We present a case of TXA-induced anaphylaxis in a 69-year-old woman who attended for elective revision of left total hip arthroplasty. Drugs used included lidocaine for local anesthesia, intravenous (IV) midazolam, and a combination of bupivacaine and diamorphine for spinal anesthesia and chlorhexidine skin preparation. A total of 200 mg of IV TXA was administered (100 mg/mL; Bowmed Ibisquus, Wrexham, UK). Two minutes after TXA, 5 minutes after spinal anesthesia, and 15 minutes after lidocaine and midazolam the patient developed generalized flushing, tachycardia (heart rate 173 bpm), and hypotension (blood pressure 42/16 mm Hg) quickly followed by cardiac arrest. Cardiopulmonary resuscitation with 400 µg IV adrenaline (epinephrine), hydrocortisone, and chlorphenamine was administered followed by a noradrenaline (norepinephrine) infusion. Serial serum tryptase level measurements at 50 minutes, 3 hours, and 24 hours (baseline) after the episode were 53.2, 67.1, and 9.1 ng/mL, respectively (normal <11.4 ng/mL). She was discharged from the intensive care unit a few days later with no functional deficit or complications. Interestingly, 1 year previously, she had also developed transient hypotension 5 minutes after administration of TXA under general anesthesia during total hip arthroplasty. All IV anesthetics and opioids had been given more than 10 minutes before TXA; hypotension responded to metaraminol with no sequelae. Patient had a history of gastroesophageal reflux disease and wasp venom anaphylaxis, but no other known allergies.

Two months after the reaction, skin prick tests (SPT) with chlorhexidine 5 mg/mL, lidocaine 10 mg/mL, bupivacaine 2.5 mg/mL, midazolam 5 mg/mL, and latex (ALK, Hørsholm, Denmark) were negative. Subsequent intradermal tests (IDT) with chlorhexidine 0.002 mg/mL, lidocaine 1 mg/mL, bupivacaine 0.25 mg/mL, and midazolam 0.5 mg/mL were also negative. Drug provocation tests (DPT) with subcutaneous 1 mL

lidocaine 10 mg/mL and bupivacaine 2.5 mg/mL were uneventful. SPT with TXA 100 mg/mL, 10 mg/mL, and 1 mg/mL were all positive with 4 mm, 3 mm, and 4 mm weals, respectively. IDT with TXA 1 mg/mL, 0.1 mg/mL, and 0.01 mg/mL were also all strongly positive with weal expansions from 3 mm to 17 mm, 3 mm to 11 mm, and 5 mm to 7 mm, respectively. Serum basophil histamine release assay (BHRA) was negative to TXA.

The immediacy and multiorgan nature of this patient's reaction with raised acute serum tryptase and positive SPT and IDT suggests anaphylaxis to TXA. All other perioperative agents were unlikely triggers based on the anesthetic chart review and the relevant SPT, IDT, and DPT. BHRA could be negative due to a low level of specific IgE to TXA or the delay between the index reaction and testing. Alternatively, patients may be allergic to TXA metabolites rather than the index drug itself. Finally, the allergic mechanism may have been non-IgE-mediated, which is unlikely considering highly elevated acute serum tryptase and positive SPT and IDT.¹ The patient was advised to avoid TXA and all other antifibrinolytic lysine derivatives. A medical alert bracelet was recommended. Subsequent hip arthroplasty was performed uneventfully without any antifibrinolytics.

TXA (trans-4-aminomethyl-cyclohexane-carbonic acid) was synthesized in the 1960s. It is a synthetic lysine amino acid derivative that exerts its antifibrinolytic effect by binding and blocking the lysine-binding sites on plasminogen molecules and thereby preventing fibrin degradation.² TXA is widely used in the hospital setting but also available prescription free in some countries that might act as a potential source of sensitization. It is included in the World Health Organization Model List of Essential Medicines³ because of a great body of evidence for its efficacy in menorrhagia, postpartum hemorrhage, hereditary bleeding disorders, for example, hemophilia, von Willebrand disease, and reduction of perioperative blood loss.² Moreover, because of downstream inhibition of bradykinin production by TXA, it is used to prevent attacks of hereditary angioedema and other types of angioedema without weals.⁴

Contraindications to TXA are few, including ongoing acute venous/arterial thrombosis, or drug hypersensitivity. Despite its frequent use, hypersensitivity reactions have seldom been reported. The first case of TXA-related anaphylaxis was published in 2004.⁵ The diagnosis was supported by a positive SPT (stock concentration) to TXA. However, the acute serum tryptase level was not raised and BHRA was negative. SPT were negative in 10 nonallergic controls suggesting a nonirritant concentration. Three cases suggestive of an IgE-mediated reaction (no allergy workup) and one of a delayed cutaneous reaction were reported in 2010.⁶ The most recent case was in a patient with an elevated baseline tryptase level with cosensitization to ondansetron and ketamine. No DPT were undertaken to exclude the role of these drugs in anaphylaxis. IDT was only performed down to a 1/500 dilution of TXA; specific IgE to TXA was not detected.⁷ These cases highlight the importance of

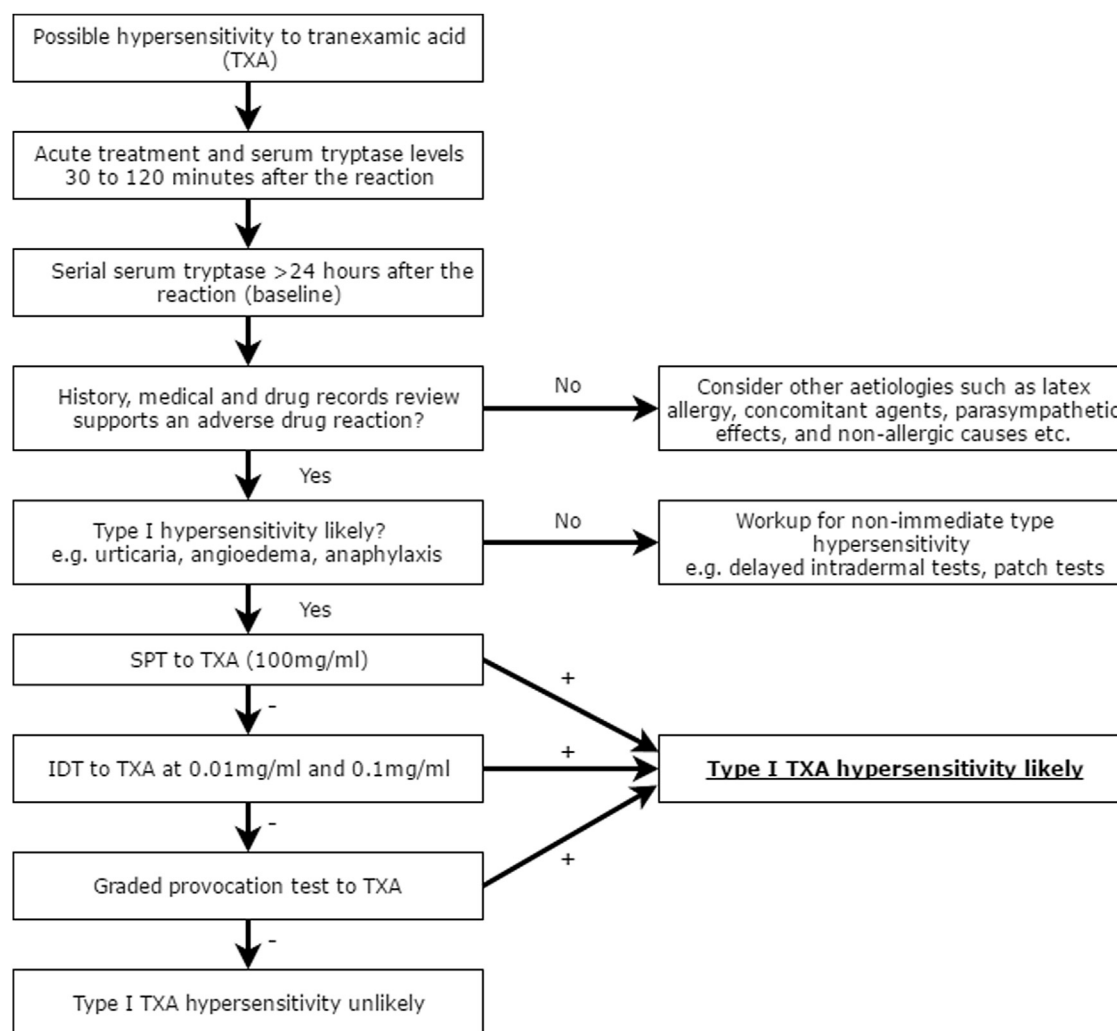


FIGURE 1. Protocol for the investigation of suspected reactions to TXA. *IDT*, Intradermal test; *SPT*, skin prick test.

a thorough clinical review and targeted allergy testing in establishing a correct diagnosis.

We propose a standardized protocol for the investigation of a suspected anaphylactic reaction to TXA (Figure 1). It entails the relevant medical and drug records review, SPT with a stock concentration of TXA (100 mg/mL) followed by, if negative, IDT with TXA at 0.01 mg/mL and 0.1 mg/mL. A single- or double-blinded DPT can be considered if necessary. A graded oral DPT might be preferred for safety reasons, but it is important to note that bioavailability of oral TXA is only 34%.⁸

Therefore, an IV DPT can also be considered in the correct clinical setting. No validated DPT protocols and no data on cross-reactivity of TXA currently exist. In confirmed cases of hypersensitivity, TXA must be avoided and alternative methods/agents for hemostasis should be sought. On the basis of the similarities of the chemical structures and potential common epitope(s), we suggest that other lysine derivatives such as aminocaproic acid should also be avoided (Figure 2). If a hemostatic drug is needed, a chemically distinct agent etamsylate has been used successfully in previous reports.⁶ Close communication

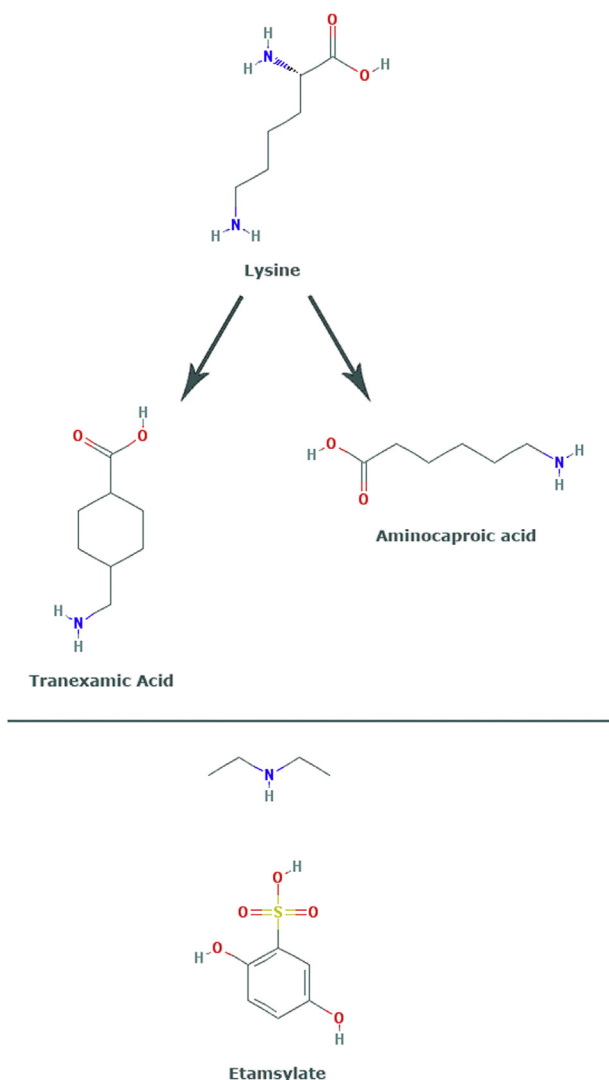


FIGURE 2. Antifibrinolytic lysine derivatives.⁹

with the patient and his or her surgeon/physicians is crucial. The allergy/immunology community should be educated about the risk of immediate hypersensitivity to TXA. Further studies are

required to validate the optimal drug concentration for skin testing and DPT protocols, as well as to identify allergenic epitope(s) of TXA and its metabolites.

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