

## **Anaphylaxis to Tranexamic Acid: 2 Cases Confirmed by Drug Provocation Test, What about Skin Tests?**

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Tranexamic acid (TXA) is an antifibrinolytic of the aminoacid lysine derivative agent which blocks the lysine binding sites on plasminogen.

TXA is used to treat heavy bleeding, such as menometrorrhagia, postpartum haemorrhage, haemophilia; to reduce the risk of death in bleeding trauma and traumatic brain injury (CRASH-2 and CRASH-3 [1]); or to prevent excessive blood loss during surgery.

There are only a few cases of TXA anaphylaxis, the first of which was described in 2004 [2]. We report the first cases of positive drug provocation test (DPT) in a TXA anaphylaxis.

#### Case 1:

A 15-year-old female with antecedent of asthma and hay fever was referred to the Allergy unit for an anaphylaxis during a knee ligamentoplasty. Preoperative IV treatments were 2g Cefazolin and 1g TXA (Exacyl®)(first exposure). A few minutes later, she developed tachycardia (heart rate 160 bpm) and bronchospasm with desaturation, which were treated by saline volume expansion, aerosol of adrenaline and methylprednisolone. The surgery was postponed. Tryptase was not measured.

Two months after the reaction, skin prick tests (SPT) and intradermal tests (IDT) were performed according to the guidelines [3].SPT with iodinated povidone, chlorhexidine and latex were negative. STP, IDT and DPT (1 g cumulative dose (CD)) with cefazolin were negative.

SPT with TXA (IV Exacyl®) (Sanofi-Aventis France) 100 mg/mL (undiluted) was negative. IDT with TXA[0.1, 1, 10 mg/mL] were negative. The IDT wheal increased from 3 to 5 mm and was surrounded by a 9 mm erythema 20 minutes later at 10 mg/mL.

An oral DPT was performed to TXA (oral solution Exacyl® 1 g/10 mL) with gradually increasing doses every 20 minutes (1 mg, 10 mg, 100 mg, 500 mg, 1000mg). The patient signed an informed consent form. The patient presented with rhinoconjunctivitis, retroauricular itching, abdominal wheals and cough 20 minutes after the eliciting dose of 100mg (111mg CD), treated with dexchlorpheniramine and salbutamol.

#### Case 2:

A 56-year-old male with antecedent of knee arthroscopy was referred for an anaphylaxis during a total knee replacement. Induction of anaesthesia was performed with propofol, sufentanil, atracurium and ketamine. Dexamethasone, 1g TXA (Exacyl®) and cefazolin were administered 20 minutes after. Within 20 minutes, she developed hypotension (blood pressure 57/35 mmHg), tachycardia (heart rate 99 bpm), desaturation (90%) and erythema treated by saline and colloid volume expansion, 150 µg IV noradrenaline, 100 µg IV adrenaline and methylprednisolone. Surgery was postponed. Serum tryptase level was raised to 14.2 µg/L 90 minutes after onset of reaction, with a baseline at 4.6 µg/L (N<13.5 µg/L). Histamine level was measured at 26.2 nmol/L per reaction and at 10.1 nmol/L (N<10nmol/L) 90 minutes after the beginning of symptoms.

Six months later, IDT with propofol 1 mg/mL, sufentanil 0.5 µg/mL, atracurium 0.01 mg/mL, ketamine 1 mg/mL, dexamethasone 0.04mg/mL and cefazolin 2 mg/mL were negative. Specific IgE to latex and quaternary ammonium ions were also negative on ImmunoCAP (<0.10 kUA/L). DPT to cefazolin (1g CD) and dexamethasone (4mg CD) were negative. SPT with undiluted TXA and IDT with TXA (Exacyl®)[10, 100 mg/mL] were performed. IDT with TXA100 mg/mL was

positive: the wheal increased from 4 to 10 mm and was surrounded by 45 mm erythema after 20 minutes.

IV DPT to TXA (Exacyl®) was performed with prior signed patient informed consent. Six minutes after the 50 mg dose (57.2 mg CD), the patient developed tachycardia (heart rate 104 bpm), cough, conjunctivitis and erythema treated with antihistamine and prednisolone.

Subsequent surgery was performed with propofol, sufentanil, atracurium, ketamine and cefazolin. No adverse effect occurred.

The two cases were reported to our regional pharmacovigilance centers.

TXA belongs to the World Health Organization (WHO) Model List of Essential Medicines since the 2011 adult edition [4]. This drug, amongst others that affect coagulation, is recommended due to its efficiency in gynaecology, haematology and surgery. For the past ten years, increasing TXA adverse effects, including hypersensitivity, are reported in VigiBase (<http://www.vigiaccess.org>), the WHO global database of individual case safety reports. It may be linked to recent recommendations (CRASH-2 and CRASH-3 [1]). In a large study carried out in 2016 in UK, TXA was the most common drug used (5.9% of all cases) in perioperative care among drugs affecting coagulation [5].

Up to now, all previous published reports of anaphylaxis to TXA have been set on medical history, skin tests and in vitro tests (table 1), but DPT have never been realised in anaphylaxis cases. Spanish guidelines recommend SPT with undiluted TXA and IDT with TXA 10 mg/mL as the nonirritant concentrations [6].

To begin with, we performed IDT with TXA up to 10 mg/mL in the first case and up to 100 mg/mL in the second case; and performed DPT due to discrepancies in skin testing recommendations.

Then, to address this gap in the literature, we performed IDT with several TXA concentrations in healthy controls. We started with TXA 100 mg/mL, but rapidly stopped because 6/6 were positive. After that, we performed TXA 10 mg/mL, but also stopped because of 2/11 positive results. Finally, we tested TXA 2 mg/mL, and 14/14 were negative. Despite previous studies [6, 7], our study has shown that IDT with undiluted TXA should not be performed because of an irritating concentration, and IDT with TXA 10 mg/mL should be carefully interpreted because of a risk of false positive results. If TXA anaphylaxis is suspected, we suggest performing SPT with undiluted TXA and IDT up to 2 mg/ml, followed by, if negative, DPT.

Due to similar chemical structures and potential common epitopes, other lysine derivatives such as aminocaproic acid should be avoided [8]. Etamsylate seems to be a safe alternative [7–9].

Our study draws attention to a growing anaphylactic risk due to the rise in use of TXA, especially for trauma patients and in cardiac and orthopedic surgery. Each case should be referred to an allergist to perform appropriate skin tests and DPT if needed.

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### **Conflicts of Interest**

The authors declare that they have no conflicts of interest.

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## Tables

**Table 1.** Skin testing and biological assessments of immediate hypersensitivity to TXA in previous published reports

| Age | Procedure               | Immediate-type reaction                          | Skin test results  | In vitro tests            | Reference |
|-----|-------------------------|--|--|---------------------------|-----------|
| 69  | Total hip arthroplasty  | Flushing, cardiac arrest                         | SPT positive with 1 mg/mL<br>IDT positive with 0.01 mg/mL  | BHRA : negative           | [8]       |
| 80  | Total knee replacement  | Hypotension, tachycardia                         | SPT positive with 100 mg/mL<br>IDT positive with 0.2 mg/mL<br><i>SPT and IDT negative in 5 healthy controls with 100 mg/mL</i> | TXA-specific IgE negative | [7]       |
| 72  | Coronary artery bypass  | Flushing, desaturation, hypotension, tachycardia | SPT positive with 100 mg/mL<br><i>SPT negative in 10 healthy controls with 100 mg/mL</i>                                       | BHRA : negative           | [2]       |
| 58  | Unknown                 | Unknown  | SPT negative with 100 mg/mL<br>IDT positive with 100 mg/mL<br>IDT negative with 10 mg/mL                                       | None                      | [9]       |
| 15  | Posterior spinal fusion | Hypotension, tachycardia                         | SPT positive with 100 mg/ml<br>IDT positive with 10 mg/ml  | None                      | [10]      |

Abbreviations: SPT: skin prick test, IDT: intradermal test, BHRA: Serum basophil histamine release assay, TXA: tranexamic acid