



## NOTE

Surgery

# Suspected anaphylactic shock associated with administration of tranexamic acid in a dog

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**ABSTRACT.** A 10-year-old male castrated Maltese was referred with clinical signs of hematuria, stranguria, and pollakiuria. The dog was diagnosed with sterile hemorrhagic cystitis with urethroliths and cystoliths. To remove the uroliths, the dog underwent retrograde urohydropropulsion followed by a cystotomy. The following day, persistent bleeding in the urinary bladder was identified with large hematoma, hematuria and anemia. In order to reduce bleeding, the dog received 10 mg/kg of tranexamic acid (TXA) intravenously. Immediately after TXA administration, the dog developed anaphylactic shock manifested by hypotension, hypothermia, tachycardia and a dull mentation. Thus, an emergency treatment including bolus injection of crystalloid, administration of dexamethasone and diphenhydramine, and oxygen supplementation was given, after which the dog quickly recovered within a few minutes.

**KEY WORDS:** anaphylactic shock, dog, hypotension, persistent bleeding, tranexamic acid

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Tranexamic acid (TXA) is an antifibrinolytic agent that exerts its effects by reversibly binding to the lysine sites on plasminogen molecules and inhibiting plasmin [13]. It is used to prevent excessive blood loss in patients during surgery and to minimize the need for blood transfusion [9, 20]. In veterinary medicine, TXA has been used to reduce blood loss by slowing fibrinolysis in various diseases causing clinical bleeding such as hemoperitoneum, hemothorax, thrombocytopenia, anticoagulant rodenticide intoxication, peri-operative bleeding, epistaxis, and feline interstitial cystitis-associated bleeding [7]. It has a wide safety margin and is rarely associated with hypersensitivity reactions [1]. In humans, common side effects of TXA are mild symptoms including nausea, flushing, vomiting, allergic skin reactions and headache, although anaphylactic shock is rarely reported [1, 2, 4–6, 11]. In dogs, there has been no report of adverse reaction to TXA except for vomiting [7].

The purpose of this case study is to report an episode of anaphylactic shock that occurred after IV administration of TXA to reduce bleeding in a dog with hemorrhage in the urinary bladder. To the author's knowledge, this is the first report of anaphylactic shock associated with TXA in a dog.

A 10-year-old, 3 kg, castrated male Maltese was admitted with one day history of hematuria, stranguria, and pollakiuria. On presentation, the dog was quiet, alert, and responsive, and the vital parameters were within normal limits including normal heart rate (132 beats/min), normotension (systolic 126 mmHg), normal respiratory effort and rate (36/min), and normothermia (38.9°C). Mucous membranes were pink with normal capillary refill time of <2 sec. Medical history of the patient revealed frequent use of steroids for atopic dermatitis due to food allergy.

Abdominal radiography and ultrasonography images showed multiple uroliths in the urinary bladder and penile urethra. Additionally, urinary bladder wall was thickened and irregular, with 2.5- to 3-mm thickness, and multiple hyperechoic materials without acoustic shadowing were observed in the urinary bladder. A free-catch urinalysis was performed. The urine specific gravity was 1.040, and a dipstick analysis revealed pH 6.0 and >250 RBCs/ $\mu$ l. Bacteriologic culture of a urine sample obtained by cystocentesis yielded negative results. Complete blood count and serum chemistry revealed no remarkable findings except mild neutrophilia (12,070/ $\mu$ l [reference interval 2,960–11,640/ $\mu$ l]) and elevated creatine kinase (311 U/l [reference interval, 12–200 U/l]). Coagulation profile and d-dimer were within normal limits. Based on these results, the dog was diagnosed with uroliths and sterile hemorrhagic cystitis.

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**Fig. 1.** Uncontrolled hemorrhage of the urinary bladder is identified by visual and ultrasound findings. (a) Hematuria is observed through the urethral catheter and urine bag. (b) Abdominal ultrasound reveals the 12.9 × 18.4 mm hyperechoic mass in the urinary bladder after cystotomy.

The dog was treated surgically with retrograde hydropropulsion followed by a cystotomy.

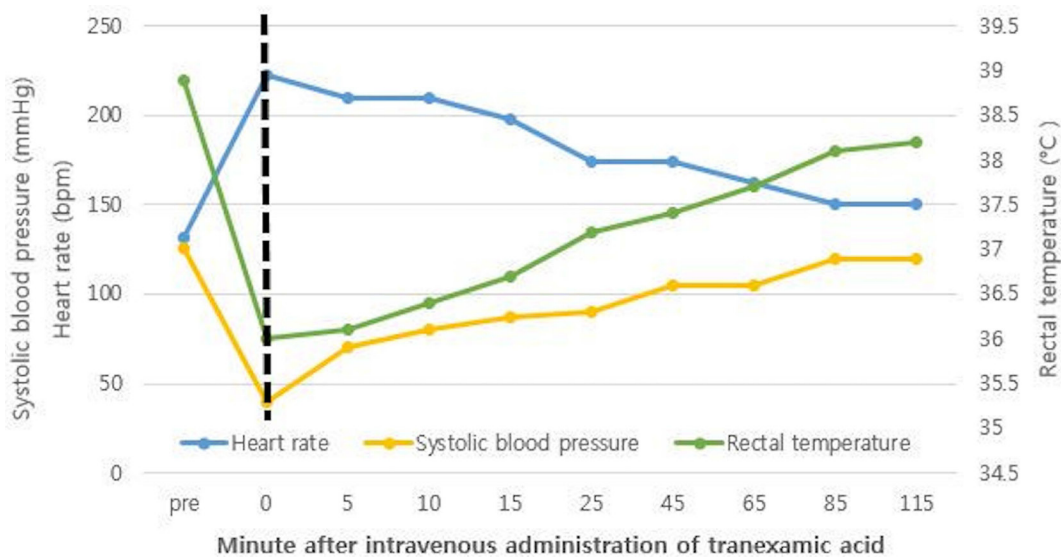
During cystotomy, multiple blood clots and uroliths were identified in the lumen of urinary bladder, and the mucosal wall of urinary bladder was generally edematous and hyperemic. All uroliths were removed successfully and no additional uroliths were observed on postoperative radiography and ultrasonography. The uroliths were confirmed as comprising calcium oxalate without any infectious organisms.

Postoperatively, the dog did not urinate spontaneously for about 8 hr. Therefore, a urethral catheter was placed, and gross hematuria was identified (Fig. 1a). Urinalysis revealed >250 RBCs/ $\mu$ l with 25 WBCs/ $\mu$ l and pH 7. Abdominal ultrasound showed a mass considered to be a hematoma inside the urinary bladder obstructing the bladder neck. The size of mass gradually increased from 13 × 12 mm to 12.9 × 18.4 mm for 2 days postoperatively (Fig. 1b). PCV consistently decreased from 39% preoperatively to 32% postoperatively followed by 28.2% for 2 days after surgery.

Since the above results suggested persistent intra-bladder hemorrhage, TXA was administered intravenously (IV) for achieving hemostasis. A total of 10 mg/kg TXA was slowly IV administered intravenously over 3 min. Two minutes later, the patient collapsed suddenly with excessive drooling and decreased mental status. Physical examination revealed pale mucous membranes with delayed capillary refill time (>2 sec), weak femoral pulse, and tachycardia (heart rate 222 beats/min). Hypothermia (rectal temperature of 36.0°C) and hypotension (systolic blood pressure 40 mmHg) were also identified. The arterial blood pressure was measured by Doppler ultrasonic flow probe. Dexamethasone (3 mg/kg IV) and diphenhydramine (2 mg/kg IM) were administered immediately with a bolus administration of 20 ml/kg isotonic crystalloid IV. Oxygen supplementation was provided via flow-by until recovery. The dog's vital parameters were monitored at 5 min intervals and the dog recovered gradually: within 5 min of initiating emergent treatment, the dog became responsive with improved mental status, and blood pressure increased to systolic 70 mmHg; after 15 min, heart rate decreased to 170/min, rectal temperature increased to 37.2°C, and systolic blood pressure was 90 mm Hg. After 15 min, the dog was completely stabilized and all vital parameters returned to normal limits (heart rate 150 beats/min, systolic blood pressure 120 mmHg, rectal temperature 38.1°C) (Fig. 2).

Seven days after surgery, the dog was fully recovered with normal urination and no further hematuria was observed. The size of hematoma consistently decreased. At a 3 month follow-up visit, the dog was apparently healthy without any complications associated with the adverse drug reaction (ADR) or cystotomy.

In the case described here, acute onset of cardiovascular collapse including tachycardia, hypotension, and changes in consciousness appeared immediately after IV administration of TXA. No other possible causative agents were administered to the dog within 6 hr of the anaphylactic reaction. Further, the dog had been apparently healthy despite persistent bleeding from the urinary bladder, and there were no significant abnormalities on daily physical examinations and blood work. There were no life-threatening comorbidities in this patient. Therefore, considering the dog's medical history, general physical condition, and timing of the symptoms, we regarded the dog's sudden collapse as anaphylactic shock from the TXA injection. In particular, the dog had a 68% reduction in systolic blood pressure immediately following the TXA injection, and this is consistent with clinical criteria for anaphylaxis, which suggests that a 30% or more reduction in systolic blood pressure after exposure is likely to be associated with anaphylaxis [15]. The dog was also assessed using the Naranjo ADR probability scale, which determines the causality connection and probability of ADR using four categories: definite, probable, possible, and doubtful. The dog in this case was determined to be in the probable category, which indicates a significantly higher likelihood of ADR [12]. In the human study that reported ADR after TXA injection, three out of five cases were identified as definite and two cases were identified as probable on the Naranjo ADR scale [6, 12].



**Fig. 2.** Changes in vital parameters including heart rate, systolic blood pressure, and rectal temperature after intravenous administration of tranexamic acid in a dog with uncontrolled hemorrhage of the urinary bladder. A black dotted line indicates the time when tranexamic acid is administered.

The dog had no history of administration of TXA or other synthetic analog of lysine, and it was this first exposure to TXA that led to anaphylactic shock. The pathogenic mechanism of this kind of anaphylaxis is non-immunologic anaphylaxis, previously called anaphylactoid reaction, which is a sudden and massive degranulation of mast cells or basophils, without involvement of IgE, that occurs at the first exposure without prior sensitization to the agents [16, 18]. Another pathogenic mechanism of anaphylaxis is an immunologic anaphylaxis, which is an IgE-mediated reaction caused by re-exposure to the specific allergens [16, 18]. According to the previous human study, TXA anaphylaxis was associated with both pathogenic mechanisms; in some patients, immunologic anaphylaxis was considered to have occurred due to previous exposure to TXA, and one of them tested positive on an intradermal test of TXA despite having no prior history of exposure; thus, the patient was considered to have immunologic anaphylaxis with previous unknown sensitization or cross-reacting molecules; in another patient, non-immunologic reaction was considered because the patient had no history of exposure [6]. In this dog, non-immunologic anaphylaxis is considered first; however, immunologic anaphylaxis is still considered a possibility in because prior history of TXA exposure cannot be completely ruled out due to limitation of full comprehension of medical history in animals. Therefore, it should be noted that anaphylactic shock associated with TXA may occur at the first administration regardless of prior sensitization to the drug in dogs.

The dog in this case had atopic dermatitis, which is known to increase the risk of anaphylactic events [3]. Atopic dermatitis is thought to aggravate both immunologic and non-immunologic anaphylactic reactions because the mastocytosis caused by long-term exposure to the allergen may result in a more massive degranulation in non-immunologic anaphylaxis. Alternatively, TXA, a synthetic analogue of lysine involved IgE binding of the allergens, may have stimulated the IgE-mediated hypersensitivity by promoting binding of the persistent allergen to IgE. Therefore, a dog with anaphylaxis risk factors, such as the allergic dermatitis in the dog described in this case, should be carefully monitored after TXA administration due to a higher risk of developing ADR following TXA administration.

Several reports concerning anaphylactic reaction to TXA have been documented in human beings, but there have been no similar reports in animals [4, 10, 11]. The symptoms of anaphylaxis related to TXA injection were variously reported as cutaneous signs including itching, erythema, and facial angioedema; respiratory disturbances; and cardiovascular collapse such as hypotension, tachycardia, and cardiac arrest [4, 6, 10, 11]. Interestingly, anaphylactic shock such as hypotension and tachycardia occurred after IV administration of TXA in all patients [4, 10, 11]. These cases included a 72-year-old male patient undergoing coronary artery bypass surgery who presented with hypotension (systolic 60 mmHg) and tachycardia (130 beats/min) shortly after IV administration [11]; a 69-year-old woman who presented for left total hip arthroplasty and developed cardiac arrest a few minutes after treatment with TXA 200 mg intravenously [10]; and a 15-year-old male who was scheduled for T2-pelvis posterior spinal fusion and developed hypotension and tachycardia after administration of TXA bolus IV 5 mg/kg and infusion 5 mg/kg/hr [4]. In the case described by this report, severe cardiovascular collapse including tachycardia, hypotension, and loss of consciousness occurred immediately after IV administration of TXA. We also considered that IV administration of TXA could lead to direct activation of the the circulating basophils without crossing natural barriers such as the skin or gastrointestinal tract, thus leading to an immediate response in cardiovascular system [15]. Therefore, it should be noted that potentially life-threatening anaphylactic shock is likely to be associated with IV administration of TXA, and careful monitoring is required when TXA is administered intravenously. We considered that the anaphylactic reaction was related to the administered dose of TXA, but this was less likely in this case. The dog received a standard dose of TXA as described in the literature, and there have been no reports of anaphylaxis



at this dosage in dogs and cats [7, 8]. And, there was no possibility of misadministration of other medicine, because the type and status of the administered drug was confirmed by three veterinarians before and after its administration. And the problem of the TXA product was excluded because the drug manufacturer confirmed that it was the general product made by the manufacturer.

In human literature, the diagnosis of drug allergy is based on the patient's history, serum tryptase, skin testing, IgE assays, basophil activation test, and challenge testing [14]. Since the history is often not reliable, procedures are not standardized, and provocation tests are sometimes risky to patients, thus skin prick and intradermal tests are most likely to be used to evaluate the hypersensitivity safely in human beings [21]. Those tests are also used to confirm TXA anaphylaxis in human beings, and a positive response was observed in patients presenting with an anaphylactic reaction to TXA [4, 10, 11]. However, those diagnostic criteria for drug-induced anaphylaxis has not yet been established in veterinary medicine [17, 19]. The utility and value of standard criteria of human beings has not been investigated reliably in veterinary medicine, and further studies are required to apply those human criteria to dogs appropriately [17]. Therefore, in veterinary medicine, the diagnosis of anaphylaxis is based mainly on a history and clinical findings with lack of a definitive test [17, 19]. In the case described here, several laboratory examinations were recommended to the owner for the diagnosis of TXA anaphylaxis, such as serologic examination to measure blood levels of IgE and inflammatory mediators, skin prick test, and challenge testing using re-administration TXA. However, the owner declined further diagnostics for the confirmation of TXA anaphylaxis due to the lack of evidence of a valid test in veterinary medicine, risk of challenge testing and financial constraints. We informed the owner of the risk of relapsing anaphylaxis when administering TXA and similar lysine analogues.

In this dog, general emergency treatment based on the assumption of drug-induced anaphylaxis, including corticosteroid administration, antihistamine administration, bolus injection of crystalloid, and oxygen supplementation, was effective in stabilizing the dog. Since the dog developed severe tachycardia, epinephrine was not selected as an emergent drug. In previous studies reporting TXA anaphylaxis in humans, the anaphylactic shock reactions were alleviated after general anti-anaphylactic treatment such as corticosteroid, epinephrine, and antihistamine administration despite severe symptoms such as cardiovascular collapse [4, 6, 10, 11]. Based on these results, we considered that TXA anaphylaxis could be stabilized rapidly if it is recognized early and managed with appropriate emergency treatment.

Anaphylactic shock associated with TXA is rare, but has been reported in human beings, and this is the first report of this condition in a dog. In this case, the anaphylactic shock occurred after IV administration of TXA in a dog with atopic dermatitis as a comorbidity, and the reaction occurred with the first administration of the drug. In conclusion, it is important to be aware of the possibility of anaphylactic shock associated with TXA administration in dogs and to detect the related symptoms early, especially if the drug is administered intravenously to a dog having other risk factors for anaphylaxis.

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