

Tranexamic Acid–Induced Toxic Epidermal Necrolysis

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Tranexamic acid is a synthetic lysine derivative that exerts its antifibrinolytic effect by reversibly blocking lysine binding sites on plasminogen and thus preventing fibrin degradation. Tranexamic acid is useful in a wide range of hemorrhagic conditions. Because it appears to reduce rates of mortality in patients with gastrointestinal hemorrhage, an increasing number of patients with excessive bleeding, such as those with traumatic bleeding or menorrhagia, are being treated with this drug.¹⁻⁴ Tranexamic acid is usually well tolerated and has been considered a relatively safe drug at the dosages generally used. Nausea and diarrhea are the most common adverse effects.² Despite this, there have been recent reports of hypersensitivity reactions through different mechanisms (immunologic and nonimmunologic). One case of anaphylactic shock, 2 cases of urticaria/angioedema episodes, and a case of drug eruption immunologically

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OBJECTIVE: To report a case of toxic epidermal necrolysis (TEN) induced by orally administered tranexamic acid in a patient with liver cirrhosis and acute rectal bleeding.

CASE SUMMARY: A 67-year-old male with a history of liver cirrhosis due to alcohol consumption with ascitic decompensation, esophageal varices, and multifactorial renal insufficiency presented with rectal bleeding. The patient was prescribed oral tranexamic acid (1000 mg every 8 hours), with partial resolution of symptoms. Ten days after treatment with tranexamic acid began, a purplish macular rash appeared over the patient's trunk. The dose of tranexamic acid was reduced to 1000 mg every 12 hours, adjusting for renal function. In the following days the lesions extended and became confluent with blisters and epidermal necrosis. Multiple mucosal surfaces were also affected. He denied allergies to any medications and had no history of tranexamic acid exposure. Treatment with tranexamic acid was suspended and fluid replacement therapy, oral prednisone therapy (0.4 mg/kg per day), and *N*-acetylcysteine 2 g every 6 hours was started, with the empiric diagnosis of TEN. Results of a skin biopsy were compatible with TEN. Resolution of the skin lesions was favorable, but after 2 weeks the patient died secondary to acute renal failure, respiratory infection, and multiorgan failure.

DISCUSSION: TEN is a rare, severe mucocutaneous adverse reaction. Although infrequent, TEN has a significant impact on public health because of its high mortality. Its pathogenesis is unclear, but it seems to be a form of delayed hypersensitivity. To our knowledge, a well-documented case of TEN following tranexamic acid use has not been reported (MEDLINE search to June 2012). There have been recent reports of skin hypersensitivity reactions through different mechanisms (immunologic and nonimmunologic). The Naranjo probability scale indicates a probable relationship between the development of TEN and tranexamic acid use in our patient.

CONCLUSIONS: This appears to be the first report of a case of TEN that occurred in a patient being treated with oral tranexamic acid. Clinicians should be made aware of this potential severe cutaneous adverse reaction that may be caused by tranexamic acid administration.

Ann Pharmacother 2013;47:e16.

Published Online, 26 Feb 2013, *theannals.com*, doi: 10.1345/aph.1R637

nonmediated have been described.^{5,6} A literature search also revealed 2 cases of fixed-drug eruption and bullous skin eruption after tranexamic acid exposure.^{7,8}

Toxic epidermal necrolysis (TEN) is a severe, episodic, acute mucocutaneous reaction related to a variety of medications. More than 100 different drugs have been reported as potential causes. The pathogenesis of TEN is unclear, but it seems to be a form of delayed hypersensitivity.⁹

To our knowledge, a well-documented case of TEN following tranexamic acid use has not previously been reported (MEDLINE search to June 2012). We report a case of tranexamic acid-induced TEN in a patient with acute intestinal hemorrhage.

Case Report

A 67-year-old man had a history of liver cirrhosis due to alcohol consumption with ascitic decompensation, esophageal varices, and multifactorial renal insufficiency. He was admitted to another hospital because of substantial rectal bleeding secondary to colopathy due to portal hypertension, with thrombocytopenia (platelets $81 \times 10^3/\mu\text{L}$ [reference range 150-450]), creatinine 2.2 mg/dL (0.4-1.1) and anemia (hemoglobin 7.6 g/dL [14-18]). The hemorrhoidal hemorrhagic point was treated with a band and suture. The patient received a transfusion of platelets and red blood cells and was prescribed tranexamic acid orally (1000 mg every 8 hours), with partial resolution of symptoms.

Two weeks later the patient was transferred to our hospital for evaluation regarding a possible liver transplant. The doses of tranexamic acid were reduced to 1000 mg every 12 hours, adjusting for renal function. We asked the Dermatology Department to evaluate a purplish, erythematous macular rash over his trunk, which had begun 10 days after treatment was initiated with tranexamic acid.

With the exception of tranexamic acid, no new medications were added to those he had been taking for 2 years (spironolactone, furosemide, omeprazole, lactulose, and bisoprolol).

After 1 week of hospitalization at our facility, the erythematous lesions extended over the patient's face, trunk, and extremities and became confluent. Blisters and epidermal necrosis were present (Figure 1). Multiple mucosal surfaces, including mouth and genitalia, were also affected. His lips were covered with erosions and hemorrhagic crust, and erosions appeared on oral mucosa. The deepidermalization was most notable in areas of greatest friction and affected approximately 50% of the body surface. The blisters broke easily, leaving extensive areas of denuded skin. Nikolsky's sign was positive in some areas (ie, slight rubbing of the skin resulted in exfoliation of the outermost layer). According to the National Cancer Institute Common Toxicity Criteria, the skin toxicity was grade IV (grade I, slight toxicity; grade V,).¹⁰ He denied allergies to

any medications and had no history of previous tranexamic acid exposure. Treatment with tranexamic acid was suspended and fluid replacement therapy, oral prednisone therapy (0.4 mg/kg per day), and *N*-acetylcysteine 2 g every 6 hours was instituted with the empiric diagnosis of TEN. Oral prednisone therapy was given for 10 days, with gradual tapering for 2 weeks.

A skin patch test and a skin biopsy were performed to ascertain any correlation of tranexamic acid with TEN. The skin patch test was negative but results of the skin biopsy were compatible with TEN. The biopsy specimen from a bullous lesion on the patient's thigh showed epidermal atrophy, with loss of the basal layer and appearance of necrotic keratinocytes, which corresponded to an interface dermatitis. In the dermis, a slight lymphocytic infiltrate was observed (Figure 2).

The diagnosis of TEN in this case was based on symptoms, time course of the disease, and the result of skin biopsy. The initial SCORTEN severity index score (a scale



Figure 1. Areas of epidermal detachment on the lateral part of the leg.

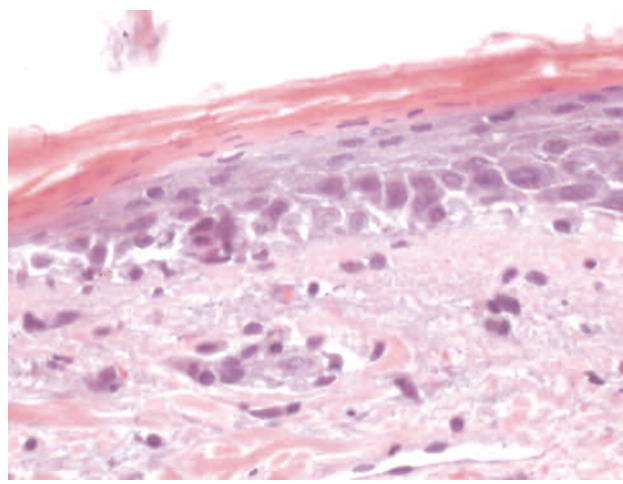


Figure 2. Biopsy showing vacuolar abnormalities at the dermal-epidermal junction, and mild lymphocytic infiltration. Sporadic necrotic keratinocytes were noted, mostly around the basal epidermis.

that determines the severity of certain bullous skin conditions) was 2 (blood levels of urea, glucose, and bicarbonate were within normal limits, as was heart rate).¹¹ A score of 0–1 is associated with mortality rates of 3.2% and a score of 5 or more with 90% mortality. Resolution of the skin lesions was favorable. The skin and mucous lesions dried and epithelial tissue was restored progressively.

Rechallenge was not considered given the severity of the clinical picture. After 2 weeks the patient developed severe hypotension, progressive deterioration of renal function, and a respiratory infection. He was transferred to the intensive care unit and dopamine perfusion with hemofiltration was begun, but with no response. The patient died secondary to acute renal failure and multiorgan failure.

Discussion

TEN is a rare, severe cutaneous adverse reaction. Although infrequent, TEN has a significant impact on public health because of its high mortality. No reliable *in vitro* test is available to rapidly identify the drugs likely to trigger the disorder. Patch tests are unsuitable for this purpose. Use of the Naranjo probability scale suggested that the adverse reaction was probably caused by tranexamic acid.¹² As is mandatory, the case was reported to the Spanish Pharmacovigilance System.

Reexposing the patient to the drug in cases like this is not acceptable, given the severity of the reaction. Consequently, the physician must rely on previously described associations and calculate the probability of each medication based on the intrinsic ability of the drug to trigger the reaction. With this report we aim to highlight that tranexamic acid is not as safe as previously thought, to report it as a drug that can trigger TEN, and to raise clinicians' awareness of the potential severe cutaneous adverse reactions caused by administration of tranexamic acid.

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Reprints/Online Access: www.theannals.com/cgi/reprint/aph.1R637

Conflict of interest: Authors reported none

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