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CASE REPORT

Hypersensitivity to tranexamic acid: a wide spectrum of adverse reactions

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Abstract *Cases description* This is a retrospective study, based on analysis of data from patients with previous adverse drug reactions admitted to the Allergy and Clinical Immunology Division of both the University of Messina and the University of Bari in the last 4 years. We observed five patients: four of them (two males and two females) with a well documented history of tranexamic acid hypersensitivity reactions and one female who showed a positive response to an intradermal challenge test with tranexamic acid. *Conclusions* Although the risk of immunogenic and severe allergic reactions to tranexamic acid is significantly lower than those associated with administration of other drugs, our experience points out that adverse reactions to tranexamic acid can occur. This drug may be responsible for a wide and various spectrum of hypersensitivity reactions characterized by different pathogenetic mechanisms (immunologic and non-immunologic). Etamsylate was a well tolerated alternative drug to tranexamic acid in all examined patients.

Keywords Adverse drug reaction · Etamsylate · Hypersensitivity · Tranexamic acid

Impact of findings on practice

- Tranexamic acid, although generally well tolerated, can cause hypersensitivity reactions through different mechanisms (immunological and non-immunological).
- Although etamsylate can cause anaphylaxis and allergic reactions, it could represent an alternative antihemorrhagic drug with a different mechanism of action respect to tranexamic acid.

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Introduction

A variety of drugs are available today to improve haemostasis and to reduce blood loss in multiple clinical syndromes: tranexamic acid, aprotinin, etamsylate (former Recommended International Non-proprietary Name, BAN: ethamsylate), vitamin K1, conjugated estrogens, desmopressin and recombinant coagulation products. Haemostatic agents can act through different mechanisms, by improving primary haemostasis, or stimulating thrombin generation and/or fibrin formation, or inhibiting fibrinolysis [1]. Tranexamic acid exerts its antifibrinolytic effect through the reversible blockade of lysine binding sites on plasminogen molecules. It is used as first line non-hormonal treatment of dysfunctional uterine bleeding, and of heavy bleeding associated with uterine fibroids, and it is also useful in the treatment of bleeding as a second line treatment, next to factor VIII, in haemophiliac patients [2]. It may be employed to prevent excessive blood loss in patients undergoing surgery and to minimise perioperative allogeneic blood transfusion [3]. It may be effective in the prophylaxis of hereditary angioedema attacks and has been reported as a possible treatment for chronic physical urticaria [1].

Antifibrinolytic drugs might be responsible for thrombotic complications and are considered as pronephritic agents because of their interference with fibrin degradation. However, there is no evidence that tranexamic acid can

increase the incidence of thrombotic complications and impairment and acute renal cortical necrosis are rare [4].

However, although tranexamic acid efficacy does not appear to be offset by serious adverse effects, its safety is poorly investigated.

There are only a few papers concerning hypersensitivity reactions to tranexamic acid. Lucas-Polomeni et al. [5] observed a case of anaphylactic shock following bolus infusion of tranexamic acid in a 72-year-old male patient undergoing coronary artery bypass graft surgery. Moreover, bullous and fixed-drug eruptions after tranexamic acid exposure have been described [6, 7].

Examination of the described five cases of tranexamic acid hypersensitivity allows to us:(a) to aware physicians about potential adverse reactions provoked by tranexamic acid administration;(b) to suggest a better-tolerated alternative drug in patients with adverse reaction to tranexamic acid needing antihemorrhagic therapy.

Cases description

This is a retrospective study, based on analysis of data from patients with previous adverse drug reactions (ADRs) admitted to the Allergy and Clinical Immunology Division of both the University of Messina and the University of Bari in the last 4 years. In most patients an oral challenge test (OCT) with an alternative molecule was performed to find an eventually suitable and well tolerated drug with similar therapeutic indications but with a different chemical structure from the drug responsible for ADR, in order to ensure patient safety. We observed five patients: four of them (two males and two females) with a well documented history of tranexamic acid hypersensitivity reactions and one female who showed a positive response to an intradermal challenge test with tranexamic acid.

Case 1

A 42-year-old man had been prophylactically treated with intramuscular tranexamic acid at a dosage of 500 mg before two separate surgery procedures (a tonsillectomy performed at the age of 8 years and a varicocelectomy at the age of 22 years). Both times, he had shown widespread itching, facial and arms edema, difficult breathing, that disappeared following corticosteroid treatment. The patient had not taken any other drugs or over-the-counter products together with tranexamic acid. Since he had to undergo surgery, he underwent OCT to etamsylate, without reaction. The patient did not mention any adverse reaction to other drugs; other possible causative factors or explanations for the reported reaction to tranexamic acid were absent.

Case 2

A 27-year-old-man, with history of adverse reaction to cephalosporins, referred to us to perform a challenge test for an alternative antibiotic drug. He mentioned an urticaria-angioedema episode associated to breathlessness induced by prophylactic intramuscular administration of tranexamic acid at a dosage of 500 mg before a previous tonsillectomy; corticosteroids and antihistamines administered at the Hospital emergency department improved these symptoms. No other drugs were taken from the patient when tranexamic acid adverse event occurred; other possible causative factors or explanations for the reported reaction to tranexamic acid were absent.

Case 3

In a 58-year-old beta-thalassemic female patient with a history of contact allergy to balsam of Peru and adverse reaction to many drugs (diclofenac, diazepam, cefprozil), cutaneous tests (skin prick test with undiluted drug and intradermal test at 1:100, 1:10 and 1:1 dilutions) with tranexamic acid were carried out. We obtained a positive result (a wide itching wheal with pseudopode emission) at the tranexamic acid intradermal administration of the 1:1 dilution (reading of test was performed 20 min after the injection). The same result was observed when the administration of tranexamic acid at the same dilution was repeated 2 hours later. The next day, the patient underwent challenge test to the alternative antihemorrhagic drug (etamsylate), without reaction.

Case 4

A 45 year-old female patient affected by a recurrent menorrhagia with a clinical history of itching maculopapular lesions located on trunk and legs as described by her dermatologist, referred to us. The reaction appeared 6 hours after the intake of one tablet of tranexamic acid at a dosage of 500 mg. No systemic or organic involvement was described. No previous contact dermatitis or sensitization to food allergens and/or aeroallergens resulted in the patient's clinical history, but 3 months before she treated a menorrhagia with a tranexamic acid treatment cycle that provoked an itching erythematous reaction on the trunk after the fourth dose. In order to find an alternative molecule with the same therapeutic effect, the patient underwent etamsylate OCT, tolerating it.

Case 5

A 60-year-old woman experienced generalized urticaria and facial angioedema 1 hour after oral administration of

tranexamic acid for excessively heavy menstrual bleeding. The adverse reaction regressed on treatment with systemic antihistamines and steroids administration at the Hospital emergency department. The clinical history of this patient was silent for inhalants and foods allergy, but she remembered a previous adverse drug reaction characterized by eyelid angioedema after the intake of a single dose of the same molecule. When hypersensitivity reaction occurred, no other concomitant drugs were taken by patient. An OCT test with etamsylate was performed without reaction.

To evaluate the causality connection between adverse reaction and tranexamic acid administrations we applied the Naranjo ADR probability scale [8]. This algorithm permits to assign the likelihood of a drug causing an unexpected event that through a ten-item questionnaire assigns numerical values to arrive at an overall total score for probability assignment. Depending on the score recorded, the causality connection may be indicated as certain, probable, possible, unlikely. The total score of our five cases was 9, 6, 8, 10 and 9, respectively, so the causality connection between adverse reaction and tranexamic acid administration was certain in the case 1, 4 and 5 and probable in the remaining two cases [8].

According to the recent findings on time of onset of hypersensitivity drug reactions, we can classify the described reactions as immediate (occurring within 1 hour after the last drug administration) in cases 1, 2 and 5, while we can consider the fourth case as a non-immediate reaction (occurring more than 1 hour after the last drug administration) [9]. In addition, we can hypothesize that in the first and in the fifth case an IgE-mediated pathogenetic mechanism is involved since, in these patients, previous contacts with tranexamic acid caused a sensitization to drug. In the third patient, the positive response to intradermal test is indicative of a type I hypersensitivity probably provoked by a previous unknown sensitization to the same or to a cross-reacting molecule. The second case is presumably supported by a non-immunologic mechanism. The typical cutaneous lesions, in association to the delayed onset of them, in the fourth case allow to consider this reaction as a cell-mediated type.

Discussion

Although the risk of immunogenic and severe allergic reactions after primary exposure or re-exposure to tranexamic acid is significantly lower than that associated with administration of other drugs such as aprotinin, our experience points out that ADR to tranexamic acid can occur [10]. According to our analysis, tranexamic acid is responsible for a wide and various spectrum of hypersensitivity reactions characterized by different pathogenetic mechanisms (immunologic and non-immunologic). It is important to outline that tranexamic acid is a synthetic analogue of lysine, the amino acid involved in IgE binding in many allergens.

The findings of our report suggest that before the assignment of a tranexamic acid treatment, physicians should take into account the potential appearance of hypersensitivity reactions.

The patients showed negative response to the OTC with etamsylate, a systemic, nonthrombogenic hemostatic agent used in medicine for over 30 years. Well-controlled clinical trials showed the therapeutic efficacy of etamsylate in dysfunctional uterine bleeding, in periventricular hemorrhage in very low birth weight babies and in surgical or postsurgical capillary bleeding [11]. Although etamsylate can cause anaphylaxis and allergic reactions, as mentioned in the summary of product characteristics, it could represent an alternative antihemorrhagic drug with a different mechanism of action respect to tranexamic acid since it does not act by fibrin stabilization but influencing the platelet adhesion and restoring capillary resistance.

Conclusion

Tranexamic acid is widely used in clinical practice but, although generally well tolerated, we believe it is important to be aware of a potential hypersensitivity to this drug especially in patients with multidrug hypersensitivity and needing antihemorrhagic therapy.

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Conflict of interest None declared.

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