CASE REPORT

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Tramadol-Induced Anaphylaxis: A Rare Case

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ABSTRACT Tramadol is frequently used to treat postoperative pain and is generally considered safe. In this case, anaphylaxis due to intravenous tramadol is presented. Left knee arthroplasty was performed on a 75-year-old patient with hypertension using an angiotensin-converting enzyme (ACE) inhibitor. The patient was administered 100 mg of tramadol for postoperative pain. Itching and redness, dyspnea, respiratory arrest, and cardiovascular collapse occurred in the patient within 1-2 minutes. The service team announced code blue, and 100 mg of methylprednisolone and 45.5 mg of pheniramine were administered intravenously with rapid fluid resuscitation. Spontaneous breathing started within 5-6 minutes of the patient who was given positive pressure ventilation, and hemodynamic recovery was observed without the need for adrenaline administration. Anaphylaxis should be kept in mind when administering tramadol, especially in patients using ACE inhibitors. It is vital to recognize anaphylaxis quickly and to start the follow-up and treatment of patients.

Keywords: Analgesics; anaphylaxis; tramadol

Tramadol hydrochloride is used to treat acute and chronic pain of moderate intensity.[1] It is generally considered a safe analgesic. The incidence of allergic reactions is less than 0.1%.[2]

According to the World Allergy Organization (WAO), anaphylaxis is a severe systemic hypersensitivity reaction that usually starts quickly and can cause death. Severe anaphylaxis is a potentially life-threatening condition in the airway, respiratory, and circulation. Food products, insect bites, and drugs are the most common causes of anaphylaxis.[3]

This case report aims to present the first reported anaphylaxis from Türkiye due to intravenous tramadol administered as an analgesic after knee arthroplasty.

CASE REPORT

The 75-year-old male patient scheduled for knee arthroplasty had no history of systemic disease other than hypertension. The patient was not using medication other than the angiotensin-converting enzyme (ACE) inhibitor Coversyl (Servier Pharma, Turkey) 5 mg 1x1. No complications were observed in the patient who was operated on under spinal anesthesia.

During the service follow-ups, 1 g paracetamol (Paracerol, Polifarma, Türkiye) and then 100 mg tramadol (Ultramex, Adeka Pharma, Türkiye) infusion in 100 ccs isotonic was started on the patient who had pain in the operation area postoperative 4th hour. Within 1-2 minutes, widespread itching, redness, respiratory distress, unconsciousness, respiratory arrest, and cardiovascular collapse developed mainly in the anterior and lateral parts of the trunk. When the patient whose breathing stopped began cyanosis, positive pressure ventilation was started with a balloon valve mask system. Code blue was announced for the patient. When the code blue team arrived (within 2-3 minutes), the tramadol infusion was terminated, and

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positive pressure ventilation was applied to the patient with a balloon valve mask system. With rapid fluid resuscitation, 100 mg of methylprednisolone (Precort, Koçak Pharma, Türkiye) and 45.5 mg of pheniramine hydrogen maleate (Infenil, INCPharma, Türkiye) were administered by the service team.

The blood pressure and pulse oximetry values of the monitored patient [electrocardiography (ECG), non-invasive blood pressure, and pulse oximetry (SpO_2)] could not be measured due to cardiovascular collapse. The patient had a heart rate of 40-50 beats min^{-1} and an unfulfilled pulse. Rapid fluid resuscitation and positive pressure ventilation with a balloon valve mask system were continued in the patient, and spontaneous breathing was observed within minutes. Hemodynamic parameters were recovered (TA: 80/50 mmHg, SpO_2: 92-96%, heart rate: 60-70 beats min^{-1}). The patient regained consciousness and had itching, nausea, and vomiting. B_2 adrenergic agonist (Brecur, Neutec Pharma, Türkiye) inhalation was applied to the patient with 2-3 L min-1 oxygen support. Hemodynamic stability was achieved within half an hour with fluid resuscitation (blood pressure: 110/70 mmHg, SpO_2: 92-98%, heart rate: 60-70 beats min^{-1}). ECG was taken from the patient and it was evaluated as usual. There was no evidence of angioedema in the mouth area of the patient, who had redness and itching in the anterior-lateral parts of the trunk. The resulting picture was evaluated in favor of anaphylaxis. Plasma tryptase, one of the laboratory findings of anaphylaxis, could not be evaluated because it was not studied in our hospital. It was learned from the patient's history that he had used paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs) before, but he did not use tramadol.

The patient was discharged after he developed anaphylaxis against tramadol and was warned not to use it in the future and to consult an allergy/immunology specialist. Written and verbal consent was obtained from the patient to share the developing picture as a case report.

DISCUSSION

Anaphylaxis represents the most severe end of the spectrum of allergic reactions. Several different definitions are used for anaphylaxis in the literature. According to the WAO Anaphylaxis Guideline (2020), the definition of anaphylaxis is shown in Table 1. Our patient observed a general itching sensation, redness, dyspnea, respiratory arrest, and cardiovascular collapse within 1-2 minutes after intravenous tramadol. According to the WAO definition, we can define the condition in our patient as anaphylaxis.

The lifetime prevalence of anaphylaxis has been reported to be between 0.3-5.1%.[4,5] It has been reported that reactions recur in 26.5-54% of anaphylaxis patients during a follow-up period of 1.5-25 years.[3] Drug-induced anaphylaxis is most commonly triggered by antibiotics and NSAIDs.

TABLE 1: Amended criteria for the diagnosis of anaphylaxis.

Anaphylaxis is highly likely when any one of the following 2 criteria are fulfilled:
1. Acute onset of an illness (minutes to several hours) with simultaneous involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula).
AND AT LEAST ONE OF THE FOLLOWING:
a. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia).
b. Reduced BP or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence).
c. Severe gastrointestinal symptoms (eg, severe crampy abdominal pain, repetitive vomiting), especially after exposure to non-food allergens.
2. Acute onset of hypotension[a] or bronchospasm[b] or laryngeal involvement[c] after exposure to a known or highly probable allergen[d] for that patient (minutes to several hours), even in the absence of typical skin involvement.

[a]Hypotension defined as a decrease in systolic BP greater than 30% from that person's baseline, OR i. Infants and children under 10 years: systolic BP less than [70 mmHg (2x age in years)] ii. Adults and children over 10 years: systolic BP less than <90 mmHg; [b]Excluding lower respiratory symptoms triggered by common inhalant allergens or food allergens perceived to cause "inhalational" reactions in the absence of ingestion; [c]Laryngeal symptoms include stridor, vocal changes, and odynophagia; [d]An allergen is a substance (usually a protein) capable of triggering an immune response that can result in an allergic reaction. Most allergens act through an immunoglobulin E-mediated pathway, but some non-allergen triggers can act independent of immunoglobulin E (for example, via direct activation of mast cells); PEF: Peak expiratory flow; BP: Blood pressure.

Anaphylaxis is an emergency that requires prompt recognition and treatment. After the removal of the triggering agent, 0.5 mg of intramuscular epinephrine is the first choice in treatment. Intravenous bolus 20 mL kg^{-1} crystalloid is recommended in patients with cardiovascular instability. Second-line drugs include B_2-adrenergic agonists, glucocorticoids, and antihistamines. Although not the first choice in anaphylaxis, it has been reported that glucocorticoids and antihistamines are mainly used.[3] In our patient, the service team used methylprednisolone and pheniramine in the literature, and a response was obtained. Although the code blue team considered administering epinephrine, it was not applied after the patient's clinical improvement began.

In acute anaphylaxis, serum tryptase levels rise from 15 minutes to 3 hours or even longer from the onset. Although high levels support the diagnosis of anaphylaxis, normal levels do not exclude anaphylaxis.[3] The WAO also recommends that patients with anaphylaxis be referred to an allergist/immunology specialist for confirmation of the suspected trigger, prevention advice, and allergen immunotherapy.

Halberg et al. said 6 cases of angioedema after oral tramadol use.[6] Tongue edema was observed in 6 patients, and edema of the upper airways was also observed in 5 patients. No urticaria or itching was observed in patients. It has been reported that 4 of the patients used ACE inhibitors.

Similarly, Grassmann reported tongue edema without skin reaction after tramadol in a patient using an ACE inhibitor.[7] The clinical status has been registered to regress within 12 hours with antihistaminic and corticosteroid treatment. The authors emphasized that the risk of tramadol-induced angioedema may increase in patients using ACE inhibitors.

From Türkiye, Küçükgöncü et al. angioedema without pruritus or urticaria were reported within half an hour after 25 mg intravenous tramadol administration in patients without ACE inhibitor use.[8]

It is not known precisely how tramadol causes angioedema. Generally, its vasodilating effect is emphasized. Tramadol causes vasodilation in vitro by directly affecting smooth muscle in rabbit aorta and increasing nitric oxide (NO) production in the endothelium.[9] It is thought that ACE inhibitors also cause angioedema by increasing vascular permeability and reducing the inactivation of bradykinin, which causes vasodilation.[10]

Mori et al. from Italy reported the only tramadol-induced anaphylaxis case in the literature.[11] A 15-year-old boy who underwent varicocele operation under general anesthesia had trunk rash, laryngospasm, glottis edema, and severe anaphylaxis symptoms requiring tracheal reintubation. He woke up from anesthesia after using tramadol. It has been reported that a rapid improvement in symptoms is observed with intravenous corticosteroids and epinephrine.

In conclusion, tramadol causes vasodilation by increasing NO production in smooth muscles and endothelium. As a result, anaphylaxis and angioedema can be seen. ACE inhibitors are also known to cause angioedema by increasing vascular permeability. Anaphylaxis should be kept in mind when administering tramadol, especially in patients using ACE inhibitors. Rapid recognition and initiation of treatment for anaphylaxis are vital. For this purpose, periodic in-hospital training will be beneficial. Patients should be referred to an allergist/immunology specialist for confirmation of the suspected trigger, prevention advice, and allergen immunotherapy.

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

This study is entirely author's own work and no other author contribution.

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