

Acute coronary syndrome due to midazolam use: Kounis syndrome during a transurethral prostatectomy

Midazolam kullanımına bağlı akut koroner sendrom: Transüretral prostatektomi sırasında Kounis sendromu

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Summary– Developments in the drugs industry are leading to more rare drug side effects being encountered in clinical practice. Of these side effects, allergic reactions and hypersensitivity are seen in the usage of a large group of drugs such as antibiotics, analgesics, antineoplastics, contrast agents, corticosteroids, intravenous anesthetics, nonsteroidal anti-inflammatory drugs, and proton pump inhibitors. One important result of these reactions is acute coronary syndrome, which may have serious life-threatening results. This syndrome was first described in 1991 by Kounis as an ‘allergic angina syndrome progressing to acute myocardial infarction’, and thereafter called ‘allergic myocardial infarction’. This case report presents a 70-year-old male who had angina and dyspnea after administration of midazolam at the beginning of a transurethral prostatectomy operation.

Özet– Klinik pratiğimizde ilaç endüstrisindeki gelişmelere paralel olarak bazı nadir ilaç yan etkilerini görmeye başladık. Bu yan etkilerden bir tanesi alerjik reaksiyon ve aşırı duyarlılıktır. Bu alerjik reaksiyon veya aşırı duyarlılık antibiyotikler, analjezikler, antineoplastikler, kontrast ajanlar, kortikosteroidler, intravenöz anestezipler, steroid dışı antiinflamatuvar ilaçlar ve proton pompa inhibitörleri gibi geniş ilaç gruplarının kullanımı sonrası görülmektedir. Bu reaksiyonların önemli sonuçlarından bir tanesi, hayatı tehdit edebilecek ciddi sonuçları olan akut koroner sendromdur. Bu sendrom ilk defa Kounis tarafından 1991 yılında, alerjik miyokart enfarktüsü olarak isimlendirilen, miyokart enfarktüsüne ilerleyen anjina sendromu olarak tanımlanmıştır. Biz burada transüretral prostatektomi ameliyatı başlangıcında uygulanan midazolam sonrası anjina ve dispnesi olan 70 yaşında erkek hastayı sunduk.

Drug hypersensitivity and allergic reactions are undesirable, sometimes life-threatening unintended reactions mediated by specific immune system cells such as mast cells.^[1,2] The real incidence of perioperative drug hypersensitivity is unknown and is difficult to estimate, but an incidence of 1 in 3,500 patients between 1988 and 1990 was reported from England.^[3] However, hypersensitivity to benzodiazepines, and particularly midazolam, is extremely rare.^[4,5]

This case report describes a case of acute coronary syndrome due to perioperative midazolam hypersensitivity in a patient with no known allergy history.

Abbreviation:

ECG Electrocardiography

CASE REPORT

A 70-year-old male was admitted to our hospital for a transurethral prostatectomy (TUR-P). After preoperative preparation, spinal anesthesia was planned for the procedure. His history was unremarkable for any allergic reaction and he had no history of diabetes mellitus, hyperlipidemia, coronary artery disease or lung disease. Only hypertension was present, and he was non-smoker.

The physical examination revealed blood pressure of 135/75 mmHg, a regular pulse of 78 beats/min and oxygen saturation of 94%. His preoperative

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electrocardiography (ECG) was sinus rhythm without any ST-T abnormalities. His lung sounds were clear and cardiac auscultation was without any murmur or extra cardiac sounds. Prior to spinal anesthesia, 2 mg midazolam was administered intravenously for pre-medication because of patient agitation. Following this, the ECG recording showed ST depression on anterior derivations (Figure 1). His blood pressure was depressed and measured 80/45 mmHg and some urti-

carial lesions were observed on the legs and back. The operation was delayed and 0.9% normal saline solution infusion was began and iv flumazenil was used for termination of midazolam effect.

The patient was then taken to the coronary intensive care unit, where he had angina and dyspnea with sweating. He was administered acetylsalicylic acid, low molecular weight heparin, atorvastatin and ranitidine for acute coronary syndrome therapy, and

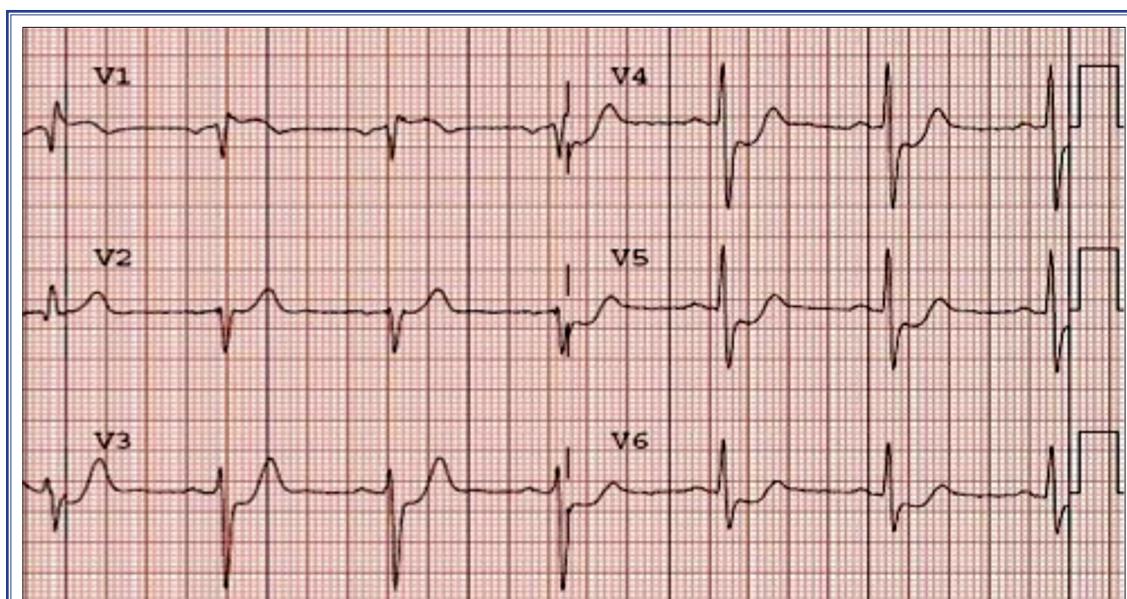


Figure 1. Electrocardiography shows ST-T depression in the anterior leads.

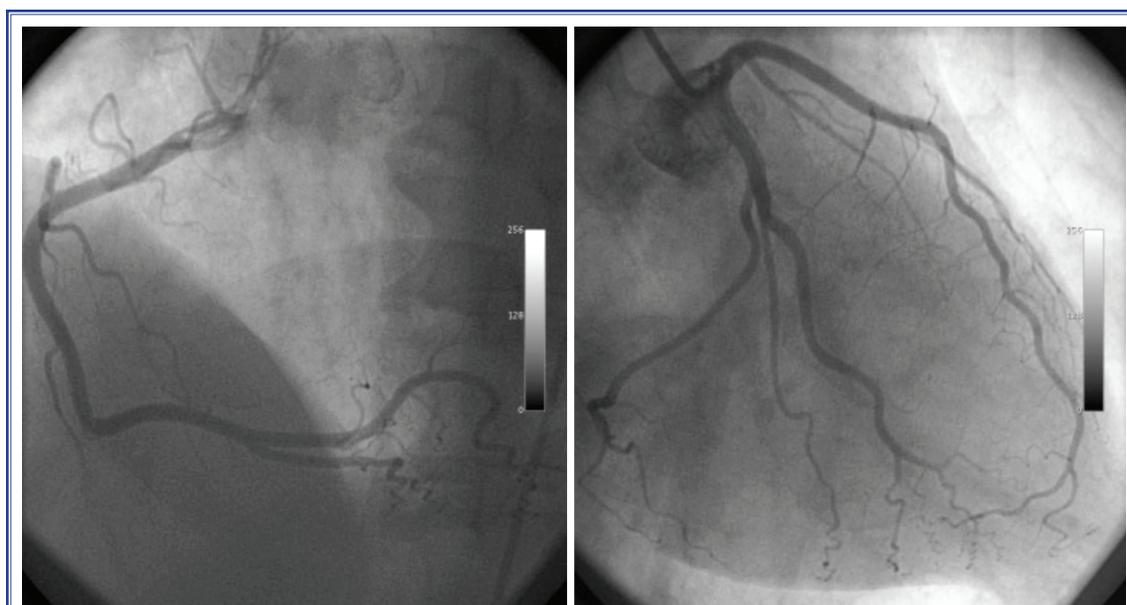


Figure 2. Angiographic images of coronary arteries.

antihistamines and corticosteroid therapy for allergic symptoms. After blood pressure returned to normal, metoprolol and ramipril were given orally to the patient. With this treatment procedure, the retrosternal chest pain and dyspnea began to improve, the urticarial lesions regressed and the patient relaxed. Transthoracic echocardiography was performed and was within normal limits and without any segmentary wall-motion abnormality.

The patient's laboratory findings, as taken in the coronary intensive care unit, were as follows: hemoglobin 11.6 g/dl, leukocytes 9600/dl, eosinophil count 5% (in normal range), creatinine 0.74 mg/dl and an elevated level of serum tryptase (16.7 µg/L). The first troponin level was 0.151 ng/dl (in normal range, 0–0.3 ng/dl) and CK-MB isoenzyme was 4 U/I. Four hours later, the control troponin level was increased, suggesting myocardial infarction (0.9 ng/dl). An emergent coronary angiography was performed, which showed normal coronary arteries with no obstructive lesion (Figure 2).

DISCUSSION

Benzodiazepines, and especially midazolam, are used intramuscularly or intravenously for preoperative sedation, anxiolysis and amnesia.^[6,7] Midazolam has many serious cardiorespiratory events and possible paradoxical reactions. Some cardiovascular side effects are premature ventricular contractions, vasovagal episodes, bradycardia, tachycardia, nodal rhythm, as well as variations in blood pressure and pulse rate.^[8] In 2012, Shrivastava reported a case of midazolam hypersensitivity causing hypotension, dyspnea, bradycardia and allergic rashes and pruritis, which was resolved using iv adrenaline, chlorpheniramine and hydrocortisone.^[9] Another case report in the literature described anaphylactic shock due to preoperative midazolam use. That case was improved by intravenous fluid, flumazenil, and steroid and antihistamine agents.^[10]

While the main pathophysiology of anaphylactoid reaction to midazolam is not clearly understood, direct nonimmune-mediated release of mediators from mast cells or direct complement activation may play a role in the process. The treatment of midazolam hypersensitivity differs according to patient status. The main methods for immediate treatment of perioperative midazolam anaphylaxis include hydration,

removal of the trigger agent and procedure abandonment. Later, alternatives may include iv adrenaline, steroids, and antihistamine agents.^[11]

The development of acute coronary syndrome after usage of allergic insult was first described in 1991 by Kounis as an 'allergic angina syndrome progressing to acute myocardial infarction', subsequently called 'allergic myocardial infarction'.^[12,13] Etiological factors, environmental agents such as insect bites, and nonsteroidal anti-inflammatory drugs, antibiotics, and anesthetic agents are most frequently associated with Kounis syndrome.^[14] The main pathophysiology in the syndrome is not completely understood, but spasm of coronary arteries due to the release of some vasoactive mediators such as histamine, platelet activating factors, chemokines and cytokines from mast cells plays a key role.^[15] These mediators can cause endothelial dysfunction, smooth muscle hypercontractility and trigger tachycardia, coronary vasoconstriction, ventricular contractility abnormalities and atrioventricular conduction blocks.^[16] Histamine is also a potent vasoconstrictive agent and triggers vasoconstriction and thrombosis. In the present case, it is possible that midazolam caused the release of histamine from mast cells, which triggered vasospasm and caused the high level of serum tryptase, helpful in determining allergic reactions.

To date, three forms of Kounis syndrome have been described. Type 1 refers to patients with normal coronary arteries without any cardiovascular risk factors in whom allergic agents trigger coronary vasospasm causing chest pain and ischemic electrocardiographic changes. Type 2 occurs in patients with existing coronary artery disease (70% of all cases), and type 3 occurs in patients with stent thrombosis, where the thrombus contains a significant amount of eosinophils and mast cells products.^[17] In clinical practice, there is no specific test for diagnosis of this syndrome. Symptoms, signs, ECG changes, transthoracic echocardiography and angiography are helpful during the diagnosis. Treatment of Kounis syndrome focuses on underlying pathology, and there are no specific protocols for treatment.

In our report, we presented a rare case of Type 1 Kounis syndrome due to usage of midazolam. In clinical practice, Kounis syndrome should be kept in mind before midazolam usage because of its serious life-threatening effects.

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