
Kounis Syndrome due to Urapidil

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Urapidil is a sympatholytic antihypertensive drug that acts as an $\alpha 1$ -adrenoreceptor antagonist and partial receptor agonist of serotonin. Kounis syndrome is a hypersensitivity coronary disorder involving the whole clinical spectrum of acute myocardial ischemia [1,2]. It is induced by exposure to drugs (especially antibiotics), food, and Hymenoptera venom [2,3]. We report a case of hypersensitivity to urapidil that seemed to manifest as Kounis syndrome.

The patient was a 71-year-old man with grass pollen allergy and a clinical history of obesity and paroxysmal atrial fibrillation that was well controlled with antiarrhythmic, anticoagulant, and β -blocker therapy. He had been accepted for hip arthroplasty with normal preoperative tests.

During the initial stage of surgery, he experienced a hypertensive crisis, which was treated. Immediately after treatment, his blood pressure dropped (60/40 mmHg), and transitory inferior and lateral ST-segment elevation were registered on the electrocardiogram (ECG). His pulse recovered spontaneously after cardiopulmonary resuscitation. Transthoracic echocardiography (TTE) revealed a minor dysfunction with inferior hypokinesia. Vasoactive drug therapy was initiated, and surgery was postponed. Hypokinesia persisted after hemodynamic stabilization, and the ST segment was normalized. Cardiac catheterization disclosed no coronary lesions, and the patient was eventually diagnosed with vasospasm of the right coronary artery. Troponin T levels were 7 ng/L (normal, ≤ 13 ng/L).

The inpatient underwent surgery a week later, with no intraoperative adverse events. During the process of awakening, while still intubated, he experienced another hypertensive event. Urapidil was administered, with immediate onset of hypotension, ST-segment elevation in the ECG, and inferior and posterior hypokinesia in the TTE. Vasoactive drug therapy and sedation-analgesia were initiated. The troponin T level was 43 ng/L. The patient remained under surveillance in the postanesthesia care unit, with no further incidents. Tryptase levels were not measured in either reaction.

The medications administered were fentanyl, propofol, rocuronium, cefazolin, chlorhexidine, midazolam, urapidil, sugammadex, and cisatracurium.

Nearly 2 months later, a perioperative hypersensitivity study was undertaken including *in vitro* and *in vivo* tests, following published recommendations for skin tests [4].

The results of skin tests with chlorhexidine, penicilloyl G and V, amoxicillin, ampicillin, cefazolin, propofol, fentanyl, midazolam, rocuronium, cisatracurium, and sugammadex were negative. There is no clear consensus regarding skin tests for antihypertensive drugs because of the low frequency of reported immediate hypersensitivity reactions [4]. Therefore, for urapidil (5 mg/mL), we proceeded with an undiluted prick test, which was positive in the patient (wheal diameter, 7 × 6 mm and local erythema) (histamine, 3 × 2 mm) (Figure) and negative in 10 controls who had never been exposed to the drug. Skin tests to propylene glycol (100 mg/mL) (pharmaceutical excipient of urapidil) were negative; the skin prick test concentration was 1/1, and those of intradermal skin tests were 1/1000 and 1/100. A basophil activation test (BAT) for urapidil yielded a negative result. A cefazolin challenge performed to enable future use of β -lactam antibiotics was without event. Total IgE was 223 kU/L. Specific IgE to latex, chlorhexidine, penicilloyl G and V, amoxicillin, and ampicillin was negative (<0.10 kU_A/L). Serum basal tryptase was 4.2 μ g/L.

Given the similarity between a series of life-threatening conditions, a differential diagnosis was made. Myocardial

infarction was initially considered but was ruled out because of the normal cardiac catheterization findings. Takotsubo cardiomyopathy was rejected. This condition is common in postmenopausal women after sudden emotional or physical stress, and the hypokinetic ventricle apex usually resolves [5]; however, this was not the case in the present report. As the patient was undergoing hip arthroplasty, another diagnosis could have been traumatic fat embolism syndrome (FES). According to Newbigin et al [6], FES is rare, usually occurring after long bone fractures or orthopedic surgery, and is described as a triad of respiratory symptoms (90%), central nervous system symptoms, and skin manifestations with confusion and petechial rash as major criteria. Given that the patient in the present case did not have these symptoms, FES was excluded. Hypovolemic shock was taken into consideration, but the patient had normal hemoglobin levels (13.2 g/dL) (normal, 13-16.5g/dL) in the preoperative blood test, which decreased to around 12.4 in the reaction in the first procedure. Such a reading is highly unlikely to provoke the abrupt hypotension recorded. In addition, before the second operation, as a preventive measure, the patient received a blood transfusion and again experienced an identical reaction. Finally, urapidil overdose was considered. As stated in the package insert [7], most adverse reactions are associated with transitory decreases in blood pressure, which resolve quickly, even while the drug continues to be perfused. Moreover, the recommended dose is 25 mg at a 20-second perfusion rate; the patient received 10 mg. Consequently, we were able to rule out overdose as a probable cause of the reactions. No cases of hypersensitivity to urapidil have been published to date, although aggravation of pre-existing psoriasis vulgaris after intake has been described [8]. Considering the chronological order of events and the negative test results, this clinical picture may suggest heart failure in the context of type I Kounis syndrome due to urapidil. Since the patient had never received urapidil, the source of sensitization is unknown. Of note, Mayorga et al [9] reported that performing BAT for various drug groups yielded an average sensitivity and specificity of 51.7% and 89.2%, respectively, although there are no references to urapidil.

The characteristic findings that reinforce this diagnosis, together with the hypersensitivity study results, are as follows [2,3]: the syndrome is more prevalent in male patients aged between 40 and 70 years; the most frequent variant is type I (72.6%), which involves coronary artery spasm with or without increased cardiac enzymes; and the right coronary artery is the most commonly affected (>50%). The ST-segment elevation suggestive of ischemia in the ECG, together with wall motion abnormalities in the distribution of the affected artery seen in the TTE and normal cardiac catheterization, strengthens our diagnostic approach. To our knowledge, this may be the first case of Kounis syndrome due to urapidil.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.



Figure. Positive prick-test for urapidil (5 mg/mL).

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