

Kounis Syndrome Due to Urapidil

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Urapidil is a sympatholytic antihypertensive drug that acts as an α_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], induced by exposure to drugs (especially antibiotics), food or hymenoptera venom [2,3]. We report a case of hypersensitivity to urapidil which is likely to manifest as Kounis syndrome.

A 71-year-old male with grass pollen allergy and medical history of obesity and paroxysmal atrial fibrillation, well controlled with antiarrhythmic, anticoagulant and beta-blocker therapy was accepted for hip arthroplasty with normal preoperative tests.

During the initial part of the surgery he suffered a hypertensive crisis which was treated. Immediately after being treated, there was a sudden drop of blood pressure (60/40mmHg) associated to transitory inferior and lateral ST-segment elevation registered on the electrocardiogram (ECG). He required cardiopulmonary resuscitation with spontaneous pulse recovery. In the transthoracic echocardiography (TTE) a minor dysfunction with inferior hypokinesia was revealed. Vasoactive drug therapy was initiated and surgery was forced to be postponed. After hemodynamic stabilization, hypokinesia persisted and the ST-segment was normalized. The cardiac catheterization disclosed no coronary lesions with the final diagnosis of vasospasm of the right coronary artery. Troponin-T levels were 7ng/L (normal ≤ 13 ng/L).

The inpatient was rescheduled for surgery a week later with no intraoperative adverse events. In the process of awakening, still with endotracheal intubation, a hypertensive event was registered once again. Urapidil was administered with an immediate onset of hypotension and ST-segment elevation in the ECG with inferior and posterior hypokinesia in the TTE. Vasoactive drug therapy and sedoanalgesia was initiated. Troponin-T levels were 43ng/L. The patient was kept under surveillance in the Reanimation 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 two months later, a perioperative hypersensitivity study was undertaken including *in vitro* and *in vivo* tests, following the published recommendations for skin tests [4].

Skin tests to 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 of antihypertensive drugs because of scarce reported immediate hypersensitivity reactions [4]. So, for urapidil (5mg/mL), we proceeded with an undiluted prick test which was positive (wheal diameter: 7*6mm and local erythema) (histamine: 3*2mm) (Figure 1) with 10 negative controls who had never been exposed to the drug previously. Skin tests to propylene glycol (100mg/mL) (pharmaceutical excipient of urapidil) were negative; the skin prick test concentration was 1/1, intradermal skin tests included concentrations at 1/1000 and 1/100, respectively. A Basophil Activation Test (BAT) for urapidil revealed a negative result. To allow future use of beta-lactam antibiotics, cefazolin challenge was performed

without event. Total IgE was 223kU/L, specific IgE to latex, chlorhexidine, penicilloyl G and V, amoxicillin and ampicillin were negative (<0.10kUA/L) and serum basal tryptase was 4.2ug/L.

In accordance with the resemblance of a variety of life-threatening conditions, differential diagnosis was considered. A myocardial infarction was initially considered which was ruled out because of a normal cardiac catheterization. A Takotsubo cardiomyopathy was rejected since it is usually suffered by post-menopausal women after sudden emotional or physical stress and the hypokinetic ventricle apex usually resolves [5] which did not happen in this case. Owing to the fact that the patient was having hip arthroplasty, another diagnosis could have been traumatic fat embolism syndrome (FES). According to *Newbiggin K., et al* [6], FES is rare, usually occurring after long bone fractures or orthopedic surgery and is described as triad of respiratory symptoms (90%), central nervous system symptoms and skin manifestations being confusion and petechial rash, respectively - both major criteria. Our patient did not manifest these symptoms so FES was excluded. A hypovolemic shock was taken into consideration but the patient presented normal hemoglobin levels (13.2g/dL) (normal: 13-16.5g/dL) in the preoperative blood test which lowered to around 12.4 in the reaction in the first surgical intervention. Such reading is highly unlikely to provoke the abrupt hypotension recorded. In addition, previous to the second operation, as a preventive measure, the patient received a blood transfusion and still suffered an identical reaction. Finally, an urapidil overdose was contemplated. As stated in the package insert [7], the majority of adverse reactions are associated to transitory descent of blood pressure readings which quickly resolve even whilst maintaining the drug perfusion. Moreover, the recommended dose is of 25mg in a 20-second perfusion rate and our patient received 10mg. Because of all of the above, an overdose as a probable cause of the

reactions was discarded. To date, no hypersensitivity cases of urapidil have been published but a case of aggravation of pre-existing psoriasis vulgaris after its intake has been described [8]. Considering the chronological order of events and the negative tests, 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 previously, the source of sensitization is unknown. It must be highlighted that BAT performed for different drug groups has been found to withhold an average sensitivity and specificity of 51.7% and 89.2%, respectively, according to some authors [9] and there are no references regarding urapidil.

The characteristic findings which reinforce such diagnosis, together with the hypersensitivity study results, are the following [2,3]: this syndrome is more prevalent in male patients with ages ranging between 40 and 70 years; the type I variant is the most frequent variant (72.6%) where there is a coronary artery spasm with or without increase of cardiac enzymes; the right coronary artery is the most commonly affected artery (>50%). 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 a normal cardiac catheterization all strengthen our diagnostic approach which, to the best of our knowledge, may result as being the first case described due to urapidil.

Conflict of Interest

None declared.

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Figure 1. Positive prick-test for urapidil (5mg/mL)

