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Caspofungin-induced fatal complete heart block: Another manifestation of Kounis syndrome

Sir,

In the very interesting report published recently in this Journal[1] a 58-year-old female patient, suffering from acute myeloid leukemia, developed bradycardia and hypotension culminating to fatal complete heart block, following a single loading dose of 70 mg of caspofungin infusion. Caspofungin was administered in an effort to treat pulmonary aspergillosis complicating severe chemotherapy-induced neutropenia. Although, in this patient, signs and symptoms of hypersensitivity were not described and tryptase and histamine were not measured an immediate hypersensitivity effect inducing transient myocardial ischemia and Kounis syndrome[2] through histamine-mediated vasospasm or an adenosine-mediated process seems possible. Kounis syndrome, initially was defined as vasospastic allergic angina syndrome, but today combines acute coronary syndromes with a variety of electrocardiographic changes ranging from ST segment elevation and depression to any arrhythmias or heart blocks. Even, the lethal coronary bare metal and drug eluting stent thrombosis is regarded as manifestation of Kounis syndrome.[3] Conditions, drugs, and environmental exposures associated with mast cell activation, involving inter-related and interacting inflammatory cells and including anaphylactic or anaphylactoid and allergic or hypersensitivity insults are the main causes of this syndrome. It is caused by preformed and newly synthesized inflammatory mediators released during the hypersensitivity inflammation. A subset of platelets bearing FcγRI, FcγRII, FcεRI and FcεRII receptors are also involved in the activation cascade.

Caspofungin acetate is echinocandin semisynthetic lipopeptide compound used for treatment of candidiasis and refractory aspergillosis. Echinocandins can act as antigens and present immediate cross-hypersensitivity suggesting that the chemical structure of cyclic peptide of these substances is the site, which is recognized by the IgE antibodies. Cross-hypersensitivity has been already described between caspofungin and the brother agent micafungin.[4] Caspofungin can induce allergic reactions such as skin rash, erythematous and purpuric macules and skin exfoliation, blisters and erosions resembling toxic epidermal necrolysis.[5] The authors of this report correctly commented on histamine releasing capacity of caspofungins. Indeed, in an experiment using cultured human mast cells and mononuclear cells taken from healthy volunteers and incubated with caspofungin it was found that caspofungin induced a significant sustained increase in histamine release.[6] Similarly, caspofungin inhibited histamine N-methyltransferase activity, an enzyme which catalyzes the inactivation of intracellular histamine.

Clinical and experimental findings have shown that hypersensitivity and anaphylaxis can induce several types of heart block. Complete heart block and myocardial ischemia has been described in a 83-year-old man who developed an anaphylactic reaction during anesthesia.[7] Transient 2:1 atrioventricular block has been reported following anaphylactic reaction to low-ionic strength computed tomography contrast agent in an elderly woman.[8] In this patient, transient prolonged QT interval was also a unique finding and it was attributed to transitory ischemia through adenosine-mediated vasospasm or a possible histamine-mediated process. Transient release in histamine levels following antigen challenge was detected in partially sensitized guinea pig hearts.[9] These colleagues were able to produce transient atrioventricular blocks in 6 of 17 sensitized hearts.

Kounis syndrome is not a rare condition but unfortunately it is rarely diagnosed despite the increasing causality. The most recent causes are the scombroid syndrome, which is called also histamine fish poisoning, the gelofusin substance, the latex material, the drug losartan, and the systemic mastocytosis with monoclonal mast cell activation syndromes. It seems likely that echinocandins acting as antigens such as caspofungins are some additional offenders. Their hypersensitivity cardiac effects should be always suspected in order to apply suitable therapeutic measures.[10]

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