J Anesth (2011) 25:790–791
DOI 10.1007/s00540-011-1187-3

LETTER TO THE EDITOR

Suspected recurrent anaphylaxis in different forms during general anesthesia: implications for Kounis syndrome

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Received: 10 May 2011 / Accepted: 2 June 2011 / Published online: 21 June 2011

To the Editor:

In the very interesting clinical report published in your journal [1], a patient who had been previously hospitalized for a right hemicolectomy for colon cancer and was readmitted for thoracotomy and resection of a right upper lobe lung mass developed, during anesthesia, coronary artery spasm and severe shock followed by a second shock with severe bronchospasm and hypotension 4 weeks later.

Although flushing or urticaria was not observed during both surgeries, tryptase levels were measured and found elevated in the second surgery. The authors of this report thought that remifentanil was the trigger of these manifestations. However, they did not refer to possible intracoronary mast cell activation [2], which sometimes is not clinically evident, but still induces the release of vasospastic, thrombogenic, and plaque-rupturing agents, including measurable serum tryptase.

The described patient had a history of hypertension with a previous surgical intervention. During general anesthesia the patient received five anesthetic drugs, namely, fentanyl, propofol, rocuronium, sevoflurane, and again remifentanil, one antibiotic, cefuroxime, and during the following resuscitation, epinephrine intravenously. Four weeks following the first anesthesia, the patient was subjected to a second surgery with the same drugs but with the addition of hydrocortisone. All these agents are known to be capable of inducing mast cell degranulation [3].

It is well known that mast cell degranulation is initiated by antigens cross-bridging their corresponding, receptor-bound antibodies on the mast cell or basophil cell surface. These cells degranulate and release their mediators when the critical number of bridged antibodies reaches the critical order of 2,000. It might be possible to accumulate the critical number of bridges by more than one non-cross-reactive antigen and its corresponding antibody. Sensitive patients simultaneously exposed to several antigens have more symptoms than do mono-sensitized individuals. A recent study reported that antibodies with different specificities can have an additive effect, and even small amounts of corresponding antigens can trigger mediator release when the patient is simultaneously exposed to them [4]. These data suggest that a possible sensitization to one anesthetic drug should not be clinically evaluated as a consequence of exposure to a single drug but rather viewed in the context of potential sensitization to multiple anesthetic agents.

Kounis syndrome [2] is the concurrence of acute coronary syndromes with conditions associated with mast cell degranulation. It is caused by inflammatory mediators such as histamine, neutral proteases, arachidonic acid products, platelet-activating factor, and a variety of cytokines and chemokines released during the activation process. It seems possible that the described patient suffered a type I variant of Kounis syndrome, which is seen in patients with normal coronary arteries but with no predisposing factors for coronary artery disease, in whom the acute release of inflammatory mediators can induce either coronary artery spasm without increase of cardiac enzymes and troponins, or coronary artery spasm progressing to acute myocardial infarction (MI) with increased cardiac enzymes and troponins.

On the other hand, type II variant of Kounis syndrome includes patients with culprit but quiescent preexisting atheromatous disease, in whom the acute release of

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inflammatory mediators can induce either coronary artery spasm with normal cardiac enzymes and troponins, or plaque erosion or rupture manifesting as acute MI. A type III variant of Kounis syndrome has been described recently and includes patients with coronary artery stent thrombosis in whom aspirated thrombus specimens stained with hematoxylin and eosin and Giemsa demonstrate the presence of eosinophils and mast cells, respectively.

This patient also received epinephrine during resuscitation. Epinephrine itself, apart from its adrenergic action, can also induce mast cell degranulation because it contains as a preservative, sodium metabisulfite. There are reports of hypersensitivity, anaphylaxis, and even death from Kounis syndrome from sulfite administration [5]. Anaphylactoid shock has been reported during epidural anesthesia for cesarean section, in which the responsible agent was metabisulfite, an additive agent of epinephrine-containing local anesthetic [3]. Therefore, a therapeutic dilemma appears in the sulfite-sensitized patient. Although epinephrine is still the primary drug for anaphylaxis, avoidance of medications that contain metabisulfites as preservatives, including epinephrine, is suggested for patients with definite sensitization to sulfites. Fortunately, sulfite-free epinephrine is now commercially available.

It should be also mentioned that corticosteroids, used in the treatment of anaphylaxis, have also been implicated as causative agents for anaphylaxis in some occasions, and this should be taken into consideration when treating such sensitized individuals [3].

Tryptase levels were measured in this patient, but assessment for reactivity to skin disinfectants and latex was not carried out. All atopic patient cases of perioperative coronary vasospasm require additional workup to identify the offending agent and to avoid future reactions. This workup should include, apart from tryptase measurements, patch testing, skin prick, and intradermal skin testing to all drugs the patient has received or is going to receive.

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