Effects of sugammadex on the coronary circulation: direct effects on coronary vessels or hypersensitivity (Kounis syndrome)?

I read with much interest the manuscript by Ko et al. [1]. The authors evaluated a case of cardiac arrest after sugammadex administration in a 76-year-old man with no notable medical history who was scheduled for robot-assisted radical prostatectomy. The cardiac arrest was followed by bigeminy-type ventricular premature contraction immediately after the sugammadex administration. Cardiac resuscitation was done successfully, and the patient was discharged uneventfully on postoperative day 8. The patient had taken several tests for the evaluation of possible coronary circulation abnormality with an impression of direct effects of sugammadex on the coronary circulation. However, the authors did not further evaluate the patient for hypersensitivity or anaphylaxis other than skin tests, which were done 4 weeks after the event.

In my opinion, I think that this case may be a sugammadex hypersensitivity event, similar to Kounis syndrome, rather than acute coronary syndrome, as the authors had described [2]. According to their report, the reasons for the diagnosis were as follows; first, fatal arrhythmia occurred immediately after sugammadex injection within 5 min; second, the typical skin lesion of hypersensitivity was not observed; third, the patient had a history of variant angina with infrequent chest pain; fourth, a positive finding of coronary circulation was obtained after recovery; and, fifth, sugammadex is not known to have any direct cardiac effects that may induce any significant hemodynamic instability or prolong the QT interval [3].

Sugammadex is now widely used in clinical practice for the selective reversal of aminosteroidal non-depolarizing neuromuscular blockers, such as rocuronium. However, sugammadex is reported to have several complications, including a hypersensitivity reaction [4]. Although several years had passed since its approval in Europe and Korea, Sugammadex was approved only in 2016 by the U.S. Food and Drug Administration owing to concerns about hypersensitivity. Tsur and Kalansky [4] described that awareness must be raised about the possibility of drug-induced hypersensitivity during the critical 5-min period immediately after the administration of sugammadex, and it was explicitly reported that most patients who developed hypersensitivity after sugammadex injection had no previous exposure to sugammadex.

I understand that many kinds and grades of drug-induced hypersensitivity reaction may possibly occur during anesthetic

care, and indeed sugammadex can be one of them. Kounis syndrome is defined as the concurrence of acute coronary syndromes with conditions associated with mast cell and platelet activation, which involves inflammatory cells in the setting of allergic reactions or hypersensitivity, and anaphylactic or anaphylactoid insults. It is known to affect persons of any age or medical condition. Moreover, although hypersensitivity reactions are normally combined with specific skin lesions, Kounis hypersensitivity-associated coronary syndrome is not accompanied by skin lesions such as skin rash, redness, erythematous wheal, or urticaria [4,5]. A definite diagnosis of Kounis syndrome, like in this case, needs to be established. Considering the patient's history, the impression of this case seems to correspond to hypersensitivity coronary syndrome or Kounis syndrome, not a direct effect on coronary circulation [5]. The preceding hypersensitivities may have affected the myocardium and coronary arteries, respectively; the first is type II, which is an inflammatory disease affecting the myocardium and the cardiac conduction system manifesting as a complication of drug therapy, and the second is type III, which is the concurrence of acute coronary syndromes associated with mast cell activation that may involve interrelated and interacting inflammatory cells. In this patient, immediate allergic screening with measurement of mast cell mediators such as histamine, tryptase, chymase, and arachidonic acid metabolites might have given further information that could have helped rule out contemporary coronary mast cell activation.

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In Response

We appreciate Dr. Yang et al's interest in our case report.

We suspect that the patient's cardiac arrest was caused by coronary spasm related to sugammadex administration. The change in the electrocardiogram before cardiac arrest showed the same pattern as for the ergonovine test, with ventricular premature contraction bigeminy [1]. If the cardiac arrest was caused by coronary spasm, the theoretical causes of coronary spasm are diverse. Although we considered the possibility of coronary spasm related to sugammadex, we could not explain the mechanism underlying this.

As hypersensitivity can also cause cardiac arrest, we performed skin tests with sugammadex, rocuronium, and rocuronium-sugammadex complex. However, the results were negative. Hypersensitivity can be evaluated with skin or blood tests. We conducted the skin tests 4 weeks after the surgery, based on recommendations made at the time of sensitization [2]. Blood tests use hypersensitivity-specific blood markers. Regrettably, we could not perform an immediate blood test for an allergic marker after the surgery. The possibility of Kounis hypersensitivity

that Dr. Yang et al. mentioned cannot be excluded, although the skin test was negative. However, the possibility of Kounis hypersensitivity caused by sugammadex was low because Kounis syndrome is accompanied by a skin rash in many cases or a positive result of skin test [3,4]. There was a recent case report about sugammadex and coronary spasm in Japan that was similar to our report [5], which concluded that sugammadex was a causative agent in cardiac arrest. Further case reports or studies on the stability and side effects of sugammadex are needed.

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