KJA
Korean Journal of Anesthesiology

Editorial
pISSN 2005-6419 • eISSN 2005-7563

Sugammadex: watch out for new side effects

Yoon-Hee Kim

Department of Anesthesiology and Pain Medicine, Chungnam National University College of Medicine, Daejeon, Korea

On December 15, 2015, the US Food and Drug Administration (FDA) approved sugammadex for the reversal of neuromuscular blockade induced by rocuronium bromide or vecuronium bromide in adults who received either of these neuromuscular blocking agents during surgery.

After its approval in Europe in 2008, sugammadex has been approved in more than 70 countries. However, the US FDA has been postponing its approval, citing concerns regarding its safety profile, including the risk of potentially life-threatening hypersensitivity reactions [1].

A recently completed clinical trial sponsored by Merck reported that the rate of anaphylaxis following administration of sugammadex did not significantly differ from that of placebo at the 95% confidence level.[1)] However, in 2014, Tsur and Kalansky [1] conducted a search of online databases and found 15 cases of possible sugammadex anaphylaxis worldwide. This number of incidents of sugammadex-related anaphylaxis is lower than that of anaphylaxis associated with neuromuscular blocking agents [2], but more accurate information on the true rate, as well as further data on affected sub-populations are needed.

Actual adverse effects that have been reported in association with sugammadex are rare. The most common adverse reactions are vomiting, dry mouth, tachycardia, dizziness and hypotension [3].

On the other hand, there has been report of severe hypotension following the administration of sugammadex, with systolic blood pressure falling to 50 mmHg or below [4].

In addition, Pühringer et al. [5] reported a relationship between sugammadex and QT interval prolongation. Many non-antiarrhythmic drugs have the adverse effect of delaying cardiac repolarization. As such, it is important to assess whether new drugs have the potential to cause QT prolongation before they go to market. However, Dahl's randomized placebo-controlled safety study of 116 patients in 2009 found that there was no relationship between sugammadex and QTc prolongation [6]. Furthermore, in de Kam et al. [7]'s randomized, double-blind, placebo-controlled trial of 84 volunteers, it was observed that there was no relationship between QT/QTc prolongation and doses of sugammadex up to 32 mg/kg.

Another adverse effect of sugammadex is severe bradycardia [8]. Consequently, the FDA recommended that patients be closely monitored for hemodynamic changes during and after its administration. Also, Saito et al. [9] reported the occurrence of transient third-degree AV block following 200 mg of sugammadex.

Another undesirable event observed in association with sugammadex administration was the development of negative pressure pulmonary edema. To explain this event, it was hypothesized that the inspiratory force created by the diaphragm may have overcome pharyngeal muscle tone and pharyngeal patency, despite a train-of-four recovery > 0.9 [10].

Additionally, Palanca et al. [11] investigated the toxicity of sugammadex on primary nerve cell cultures in rats and observed sugammadex-induced activation of mitochondria-dependent apoptosis. Although the authors pointed out that penetration of the blood-brain barrier by sugammadex was usually poor (< 3%), the results suggest potentially severe consequences in cases of inadvertent intrathecal application of sugammadex.

In the current issue of the *Korean Journal of Anesthesiology*, Ko et al. [12] reported the occurrence of cardiac arrest due to coronary artery vasospasms that occurred within 2 minutes of

[1)] Sugammadex hypersensitivity study (Study P06042) [Internet]. ClinicalTrials.gov Identifier: NCT00988065 [updated 2015 Apr 7; cited 2016 Aug 18]. Available from clinicaltrials.gov/ct2/show/NCT00988065

Corresponding author: Yoon-Hee Kim, M.D., Ph.D.
Department of Anesthesiology and Pain Medicine, Chungnam National University College of Medicine, 282, Munhwa-ro, Jung-gu, Daejeon 35015, Korea
Tel: 82-42-280-7841, Fax: 82-42-220-7968
E-mail: yhkim040404@gmail.com
ORCID: http://orcid.org/0000-0002-8282-610X

Korean J Anesthesiol 2016 October 69(5): 427-428
http://dx.doi.org/10.4097/kjae.2016.69.5.427

sugammadex administration in a patient with variant angina. The authors proposed that both hypomagnesemia and sugammadex are probable causes of coronary vasospasm, but suggested that sugammadex was the more probable cause in their case given the time course of drug administration.

In the case of anaphylaxis or anaphylactoid reactions, acute coronary syndromes, such as coronary artery spasms and acute myocardial infarctions, may occur simultaneously, a phenomenon described by Kounis in 1991 as Kounis syndrome. During an allergic event, activation of mast cells leads to the release of histamine, leukotrienes, and serotonin. These mediators impact hemodynamic functions, resulting in generalized vasodilation or coronary vasospasm [13]. However, regarding the KJA case, since the patient showed negative result from the intradermal test for sugammadex-rocuronium complex, we can assume that the symptoms were not due to Kounis syndrome. The major cause of variant angina is known to be coronary artery spasms, and histamine is known to be one of the potential mediators [14]. Histamine is known to provoke coronary artery spasms in patients suffering from variant angina, and it is also reported that the concentration of histamine is higher in these patients compared to those who are not suffering from variant angina [14]. In the KJA case, one cannot rule out the possibility that the primary cause of coronary artery spasms was sugammadex-induced non-immune histamine release. In a similar case in 2015, repetitive cardiac arrest due to coronary spasms was reported without any signs of anaphylaxis after the use of sugammadex [15].

The various side-effects reported after sugammadex use may not always be related to sugammadex. However, sugammadex has become an increasingly important option and its use will likely continue to increase. Thus, we should always take an interest in possible sugammadex-related side effects.

References

1. Tsur A, Kalansky A. Hypersensitivity associated with sugammadex administration: a systematic review. Anaesthesia 2014; 69: 1251-7.
2. Ledowski T. Sugammadex: what do we know and what do we still need to know? A review of the recent (2013 to 2014) literature. Anaesth Intensive Care 2015; 43: 14-22.
3. Welliver M, McDonough J, Kalynych N, Redfern R. Discovery, development, and clinical application of sugammadex sodium, a selective relaxant binding agent. Drug Des Devel Ther 2009; 2: 49-59.
4. Kokki M, Ali M, Turunen M, Kokki H. Suspected unexpected adverse effect of sugammadex: hypotension. Eur J Clin Pharmacol 2012; 68: 899-900.
5. Pühringer FK, Rex C, Sielenkämper AW, Claudius C, Larsen PB, Prins ME, et al. Reversal of profound, high-dose rocuronium-induced neuromuscular blockade by sugammadex at two different time points: an international, multicenter, randomized, dose-finding, safety assessor-blinded, phase II trial. Anesthesiology 2008; 109: 188-97.
6. Dahl V, Pendeville PE, Hollmann MW, Heier T, Abels EA, Blobner M. Safety and efficacy of sugammadex for the reversal of rocuronium-induced neuromuscular blockade in cardiac patients undergoing noncardiac surgery. Eur J Anaesthesiol 2009; 26: 874-84.
7. de Kam PJ, van Kuijk J, Prohn M, Thomsen T, Peeters P. Effects of sugammadex doses up to 32 mg/kg alone or in combination with rocuronium or vecuronium on QTc prolongation: a thorough QTc study. Clin Drug Investig 2010; 30: 599-611.
8. Bilgi M, Demirhan A, Akkaya A, Tekelioglu UY, Kocoglu H. Sugammadex associate persistent bradycardia. Int J Med Sci Public Health 2014; 3: 372–4.
9. Saito I, Osaka Y, Shimada M. Transient third-degree AV block following sugammadex. J Anesth 2015; 29: 641.
10. Suzuki M, Inagi T, Kikutani T, Mishima T, Bito H. Negative pressure pulmonary edema after reversing rocuronium-induced neuromuscular blockade by sugammadex. Case Rep Anesthesiol 2014; 2014: 135032.
11. Palanca JM, Aguirre-Rueda D, Granell MV, Aldasoro M, Garcia A, Iradi A, et al. Sugammadex, a neuromuscular blockade reversal agent, causes neuronal apoptosis in primary cultures. Int J Med Sci 2013; 10: 1278-85.
12. Ko MJ, Kim YH, Kang E, Lee B, Lee S, Jung J. Cardiac arrest after sugammadex administration in a patient with variant angina. Korean J Anesthesiol 2016; 69: 514-7.
13. Kounis NG, Zavras GM. Histamine-induced coronary artery spasm: the concept of allergic angina. Br J Clin Pract 1991; 45: 121-8.
14. Sakata Y, Komamura K, Hirayama A, Nanto S, Kitakaze M, Hori M, et al. Elevation of the plasma histamine concentration in the coronary circulation in patients with variant angina. Am J Cardiol 1996; 77: 1121-6.
15. Hoshino K, Kato R, Nagasawa S, Kozu M, Morimoto Y. A case of repetitive cardiac arrest due to coronary vasospasm after sugammadex administration. Masui 2015; 64: 622-7.