

RESEARCH REPORT

Association between sugammadex and anaphylaxis in pediatric patients: A nested case-control study using a national inpatient database

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Funding information

This work was supported by grants from the Ministry of Health, Labour and Welfare, Japan, the Ministry of Education, Culture, Sports, Science and Technology, Japan, and the Japan Agency for Medical Research and Development (AMED).

Section Editor: Joseph Cravero

Summary

Background: Sugammadex is used as a reversal drug during anesthesia. Although several case reports have described anaphylaxis following sugammadex infusion, little is known about the relationship between sugammadex and anaphylaxis, particularly in pediatric patients.

Aims: The aim of this retrospective study was to investigate the association between sugammadex and in-hospital anaphylaxis in pediatric patients who underwent general anesthesia.

Methods: We identified patients who underwent general anesthesia in a Japanese national inpatient database between July 2010 and March 2016. We conducted 1-4 case-control matching between patients with and without perioperative anaphylaxis. We calculated the adjusted odds ratio for sugammadex use and occurrence of anaphylaxis, using a conditional logistic regression analysis with adjustment for duration of anesthesia, antibiotics, and blood transfusions.

Results: Among 835 405 patients who underwent general anesthesia, we identified 149 (0.018%) patients with anaphylactic shock and 472 (0.056%) with a combination of anaphylaxis associated signs/symptoms and skin lesions. Sugammadex use was not significantly associated with anaphylactic shock (odds ratio, 0.80; 95% confidence interval, 0.53-1.21; $P = .29$) or the combination of anaphylaxis associated signs/symptoms and skin lesions (odds ratio, 1.25; 95% confidence interval, 0.97-1.60; $P = .08$).

Conclusion: The present study showed no significant association between sugammadex and perioperative anaphylaxis in pediatric patients who underwent general anesthesia.

KEYWORDS

anesthesia, child, claims analysis, gamma-cyclodextrins, hypersensitivity, infant

1 | INTRODUCTION

Sugammadex (Bridion®) is widely used for reversal of neuromuscular blockade in anesthesia. Sugammadex provides specific and rapid reversal of rocuronium-induced neuromuscular blockade, and has

been used in Japan since 2010. Several studies reported that sugammadex exhibited rapid action with predictable recovery in pediatric and adult patients.¹⁻³

Some reports described sugammadex-induced anaphylactic reactions in adults.⁴⁻¹⁰ A previous study reported that incidence

proportion of sugammadex-induced anaphylactic reactions was estimated to be 0.003%.⁷ However, the data were obtained from anesthesiologists on a voluntary basis, and may have been underreported. Regarding pediatric patients, only a few small studies have reported anaphylaxis after sugammadex administration.^{3,5,7}

In the present study, we examined the association between sugammadex and anaphylaxis in pediatric patients who underwent general anesthesia, using a national inpatient database in Japan. Our hypothesis was that sugammadex is associated with perioperative anaphylaxis. We tested this hypothesis using a nested case-control study design.

2 | MATERIALS AND METHODS

2.1 | Setting and participants

We conducted a nested case-control study using the Japanese Diagnosis Procedure Combination database. Details of the database were described previously.¹¹ Briefly, the database contains discharge abstract and administrative data collected from participating hospitals. The database includes data on approximately 7 million inpatients from more than 1000 hospitals every year. The database includes the following information: unique hospital identifiers; patient age and sex; diagnoses, comorbidities at admission, and complications after admission recorded with International Classification of Disease Tenth Revision (ICD-10) codes and text data in Japanese language; procedures recorded with original Japanese codes; duration of anesthesia; body weight and height; and in-hospital deaths.

Attending physicians are responsible for recording diagnoses with reference to medical charts. A recent validation study on recorded diagnoses in the database that used diagnoses in medical charts as the gold standard showed the sensitivity and specificity were 78.9% and 93.2%, respectively, for primary diagnoses.¹²

This study was approved by the Institutional Review Board at The University of Tokyo. The requirement for informed consent was waived because of the anonymous nature of the data.

2.2 | Patient selection

We identified patients under 18 years of age who underwent general anesthesia between July 2010 and March 2016. We excluded patients who had undergone general anesthesia more than once during hospitalization and those for whom the date of general anesthesia was missing.

2.3 | Outcomes

The outcome was occurrence of perioperative anaphylaxis. We defined anaphylaxis in 2 ways. First, we considered ICD-10 code T782 (anaphylactic shock, unspecified) or T886 (anaphylactic shock as adverse effect of correct drug or medicament properly administered) to denote anaphylactic shock. This definition can be regarded as “probable” anaphylaxis.

What is already known

- Anaphylaxis caused by sugammadex has typically been reported with only limited data on the basis of small samples.

What this article adds

- Using a large national database, the present study showed no significant association between sugammadex and perioperative anaphylaxis in pediatric patients.

Second, anaphylaxis was defined as a status with at least 1 skin lesion diagnosis along with at least 1 anaphylaxis associated signs/symptoms. This definition can be regarded as “probable and possible” anaphylaxis. Skin lesion diagnoses included L27 (localized skin eruption caused by drugs and medicaments taken internally), L30 (other and unspecified dermatitis), and L50 (urticaria). Anaphylaxis associated signs/symptoms included the respiratory symptoms of J02 (acute pharyngitis, unspecified), J20 (acute bronchitis), J30 (vasomotor and allergic rhinitis), J40 (bronchitis, not specified as acute or chronic), J45 (asthma), J46 (status asthmaticus), J96 (respiratory failure, not classified elsewhere), and R06 (abnormalities of breathing). As well as searching for the ICD-10 codes of T570 (cardiogenic shock), R571 (hypovolemic shock), R578 (other shock), R579 (shock, unspecified), T882 (shock due to anesthesia), and R00 (unspecified abnormalities of heart beat), we also searched for the related diagnoses of “hypotension during operation” and “tachycardia during operation” written in Japanese. The definitions of anaphylaxis associated signs/symptoms were based on the anaphylaxis guideline of the Japanese Society of Allergology, which was based on the World Allergy Organization Anaphylaxis guideline.¹³ We did not include gastrointestinal symptoms in our definition of anaphylaxis because all study patients had undergone general anesthesia and it is difficult to identify gastrointestinal symptoms such as nausea and vomiting during general anesthesia.

2.4 | Statistical analysis

We have presented age and duration of anesthesia as medians and interquartile range. We classified the type of hospital as academic or other. We determined whether any of the study patients had asthma or spina bifida or had received preoperative or intraoperative antibiotics, steroids, antihistamine, neuromuscular blocking agents, reversal drugs, or blood transfusions because these are all reportedly potential risk factors for anaphylaxis according to previous studies.^{14–17} We identified asthma and spina bifida by ICD-10 codes J45 and Q05, respectively. Neuromuscular blocking agents included rocuronium, vecuronium, and suxamethonium. Reversal drugs included neostigmine and sugammadex. We also identified all blood transfusions.

Because we collected the patient data from multiple facilities, we extracted cases and controls from the same facility in a ratio of 1:4 for the same year with the aim of canceling out site effects. That is, for each patient with anaphylaxis, we selected 4 controls of the same sex in the same age category, same hospital, and same fiscal year. If there were more than 4 matched control candidates for a particular case, we randomly selected 4 control patients. We conducted the case-control matching without replacement. We selected controls separately for analysis of the “probable” and “probable and possible” patients with anaphylaxis.

Because the cases and controls were associated in a pairwise fashion, we performed conditional logistic regression analyses to calculate the odds ratio for sugammadex and occurrence of perioperative anaphylaxis. Because there were too few patients with asthma, spina bifida, preoperative steroids, preoperative antihistamines, vecuronium, suxamethonium, or neostigmine, we did not subject these factors to multivariable regression analyses. We also excluded rocuronium because use of rocuronium and sugammadex is correlated (sugammadex is generally used to reverse rocuronium-induced neuromuscular blockade). We also excluded age, sex, fiscal year, and hospital factors because these were key variables in the case-control matching. Thus, we included duration of anesthesia, antibiotics, blood transfusion, and sugammadex as independent variables in the multivariable regression analyses.

We also have compared the baseline variables between the groups who did and did not receive sugammadex in the case-control matched samples. These are attached as Tables S1 and S2.

IBM SPSS Statistics version 22 (IBM SPSS, Armonk, NY, USA) and STATA version 14 software (StataCorp, College Station, TX, USA) were used. The threshold for significance was $P < .05$.

3 | RESULTS

We identified 846 680 patients who had undergone general anesthesia during the study period. We excluded 11 274 patients who had received general anesthesia more than once and 1 patient for whom the date of general anesthesia was missing. We thus identified 835 405 eligible patients.

The total number of deaths was 2111 (0.25%), the median length of stay was 11 days, and the number of patients who received rocuronium was 606 410 (72.6%). Of these, 367 724 (60.6%) had received sugammadex, 51 832 (8.5%) neostigmine, and 188 359 (31.1%) had not received any reversal drug.

We identified 149 (0.018%) patients with “probable” anaphylaxis (including anaphylactic shock) and 472 (0.056%) with “probable and possible” anaphylaxis (comprising anaphylaxis associated signs/symptoms combined with skin lesions).

Table 1 shows the patient characteristics in the matched case and control groups for “probable” anaphylaxis. There were no anaphylaxis cases in the suxamethonium group and only 1 case in the spina bifida group. Table 2 shows the patient characteristics in the matched case and control groups for “probable and

TABLE 1 Characteristics of patients in the matched case and control groups for probable anaphylaxis (anaphylactic shock)

	No anaphylaxis, n = 591	Probable anaphylaxis, n = 149	Total, n = 740
Age (y)			
Median, IQR (25-75)	12.8 (8.2-16.1)	13.3 (8.4-16.7)	12.9 (8.2-16.2)
Fiscal year, n (%)			
2010	54 (9.1)	14 (9.4)	68 (9.2)
2011	64 (10.8)	16 (10.7)	80 (10.8)
2012	96 (16.2)	24 (16.1)	120 (16.2)
2013	148 (25.0)	37 (24.8)	185 (25.0)
2014	117 (19.8)	30 (20.1)	147 (19.9)
2015	112 (19.0)	28 (18.8)	140 (18.9)
Male, n (%)	348 (58.9)	87 (58.4)	435 (58.8)
Academic hospital, n (%)	272 (46.0)	68 (45.6)	340 (46.0)
Duration of anesthesia (min)			
Median, IQR (25-75)	126 (89-188)	140 (104-265)	131 (91-206)
Asthma, n (%)	1 (0.2)	4 (2.7)	5 (0.7)
Spina bifida, n (%)	3 (0.5)	1 (0.7)	4 (0.5)
Antibiotics, n (%)	531 (89.9)	137 (92.0)	668 (90.3)
Steroid (preoperative), n (%)	11 (1.9)	15 (10.1)	26 (3.5)
Antihistamine (preoperative), n (%)	5 (0.9)	5 (3.4)	10 (1.4)
Rocuronium, n (%)	497 (84.1)	136 (91.3)	633 (85.5)
Vecuronium, n (%)	9 (1.5)	6 (4.0)	15 (2.0)
Suxamethonium, n (%)	9 (1.5)	0 (0.0)	9 (1.2)
Blood transfusion, n (%)	41 (6.9)	14 (9.4)	55 (7.4)
Neostigmine, n (%)	37 (6.3)	5 (3.4)	42 (5.7)
Sugammadex, n (%)	326 (55.2)	75 (50.3)	401 (54.2)

IQR, interquartile range.

possible” anaphylaxis. As can be seen in both Tables 1 and 2, the median duration of anesthesia was longer in the anaphylaxis groups.

The results of the conditional logistic regression analyses are presented in Table 3 for patients with “probable” anaphylaxis and Table 4 for patients with “probable and possible” anaphylaxis. Perioperative anaphylaxis was significantly associated with duration of anesthesia in both sets of patients. In patients with “probable and possible” anaphylaxis, perioperative anaphylaxis was also associated with blood transfusion. No significant association was found between sugammadex use and perioperative anaphylaxis in both sets of patients.

	No anaphylaxis, n = 1867	Probable and possible anaphylaxis, n = 472	Total, n = 2339
Age (y)			
Median, IQR (25-75)	8.2 (2.0-14.1)	8.2 (3.0-14.3)	8.2 (2.9-14.2)
Fiscal year, n (%)			
2010	184 (9.9)	47 (10.0)	231 (9.9)
2011	335 (17.9)	84 (17.8)	419 (17.9)
2012	307 (16.4)	78 (16.5)	385 (16.5)
2013	382 (20.5)	96 (20.3)	478 (20.4)
2014	307 (16.4)	78 (16.5)	385 (16.5)
2015	352 (18.9)	89 (18.9)	441 (18.9)
Male, n (%)	1040 (55.7)	262 (55.5)	1302 (55.7)
Duration of anesthesia (min)			
Median, IQR (25-75)	118 (82-181)	142 (103-255)	123 (85-195)
Asthma, n (%)	8 (0.4)	67 (14.2)	75 (3.2)
Spina bifida, n (%)	13 (0.7)	4 (0.9)	17 (0.7)
Antibiotics, n (%)	1590 (85.2)	430 (91.1)	2020 (86.4)
Steroid (preoperative), n (%)	37 (2.0)	33 (7.0)	70 (3.0)
Antihistamine (preoperative), n (%)	20 (1.1)	19 (4.0)	39 (1.7)
Rocuronium bromide, n (%)	1448 (77.6)	409 (86.7)	1857 (79.4)
Vecuronium bromide, n (%)	62 (3.3)	26 (5.5)	88 (3.8)
Suxamethonium, n (%)	22 (1.2)	6 (1.3)	28 (1.2)
Blood transfusion, n (%)	126 (6.8)	62 (13.1)	188 (8.0)
Academic, n (%)	974 (52.2)	244 (51.7)	1218 (52.1)
Neostigmine, n (%)	136 (7.3)	28 (5.9)	164 (7.0)
Sugammadex, n (%)	838 (44.9)	222 (47.0)	1060 (45.3)

IQR, interquartile range.

TABLE 2 Characteristics of patients in the matched case and control groups for probable and possible anaphylaxis (anaphylaxis associated signs/symptoms combined with skin lesions)

4 | DISCUSSION

The issue of whether sugammadex increases anaphylaxis during anesthesia has been under debate. One possible mechanism for sugammadex-induced hypersensitivity or anaphylaxis is that sugammadex has gamma-cyclodextrin structures, which are also included in foods and daily-use goods (flavors, certain sensitive colors, fat-soluble vitamins, polyunsaturated fatty acids).^{18,19} Another possible mechanism is that cyclodextrins may change the immunologic and allergenic behavior of the sugammadex-rocuronium complex.²⁰ In contrast, another study reported that sugammadex was useful for the management of rocuronium-induced anaphylaxis.²¹ Thus, the true mechanism for sugammadex-induced anaphylaxis remains unknown.

Clinical studies on sugammadex-induced anaphylaxis have been lacking. There have been only small studies on anaphylaxis after sugammadex infusion in pediatric patients.^{3,4} One systematic review included 5 randomized controlled studies with a total of 253 pediatric patients (129 sugammadex users and 124 controls), but this sample size was too small to evaluate the relationship between sugammadex infusion and anaphylaxis.³

The reported risk factors for perioperative anaphylaxis include age and asthma.^{14,22} Several studies have described that blood transfusion and neuromuscular blocking agents can be risk factors during anesthesia.^{17,23} Spina bifida may also be a risk factor for latex allergy.¹⁵ In the present study, perioperative anaphylaxis was associated with blood transfusions. The present study also showed an association between longer duration of anesthesia and anaphylaxis, but the causal relationship remains unknown. It was unclear whether the use of various drugs during prolonged anesthesia resulted in anaphylaxis or whether the anaphylaxis events resulted in prolongation of anesthesia.

To our knowledge, the present study is the first to examine the association between sugammadex use and anaphylaxis, using a national inpatient data. The strength of this study was the large sample size of sugammadex users and anaphylaxis cases.

In Japan, sugammadex is used most frequently, because atracurium is not sold and rocuronium is likely to be selected as a neuromuscular blocking agent. Indeed, sugammadex was used frequently in our study cohort. A previous study has shown that sugammadex was used 4 times more frequently in Japan in 2010 than in Spain; Spain has the second most frequent usage worldwide.⁶

TABLE 3 Conditional logistic regression in nested case-control study for probable anaphylaxis (anaphylactic shock)

	Odds ratio	95% confidence interval	P
Duration of anesthesia (min)			
≤59	Reference		
60-119	4.13	1.17-14.55	.03
120-179	5.71	1.58-20.73	.01
≥180	7.07	1.93-25.96	.003
Antibiotics			
No	Reference		
Yes	0.90	0.45-1.82	.78
Blood transfusion			
No	Reference		
Yes	1.18	0.56-2.46	.66
Sugammadex			
No	Reference		
Yes	0.80	0.53-1.21	.29

TABLE 4 Conditional logistic regression in nested case-control study for probable and possible anaphylaxis (anaphylaxis associated signs/symptoms combined with skin lesions)

	Odds ratio	95% confidence interval	P
Duration of anesthesia (min)			
≤59	Reference		
60-119	1.92	1.16-3.19	.01
120-179	3.15	1.84-5.38	<.001
≥180	4.24	2.45-7.34	<.001
Antibiotics			
No	Reference		
Yes	1.17	0.79-1.75	.44
Blood transfusion			
No	Reference		
Yes	2.01	1.38-2.91	<.001
Sugammadex			
No	Reference		
Yes	1.25	0.97-1.60	.08

We believe our case-control matching approach was the most appropriate given that there were very few anaphylaxis events and a very large and heterogeneous group of patients who did not develop anaphylaxis. The anaphylaxis cases were collected from multiple facilities, and up to 4 controls were extracted for each case from the same facility. These steps are important in canceling out site clustering effects; that is, patients at the same hospital are more likely to receive similar treatments and have similar responses relative to patients in other hospitals. We believe that use of a traditional logistic regression model that includes all patients would not cancel out such site clustering effects.

The present study has several limitations. First, “probable” anaphylaxis may be an underestimation, while “probable and possible”

anaphylaxis may be an overestimation, of true anaphylaxis. However, the aim of the present study was not to clarify the accurate prevalence of anaphylaxis after sugammadex infusion, but to reveal the association between sugammadex and perioperative anaphylaxis. The 2 conditional logistic regression analyses showed no significant differences, suggesting that our results of an insignificant association between sugammadex and perioperative anaphylaxis are robust.

Second, the database did not include the following information: American Society of Anesthesiologist Physical Status, severity of anaphylaxis, previous medical history, previous surgical records, accurate dosage of sugammadex, interval from sugammadex infusion to onset of anaphylaxis, and treatments for anaphylaxis. These unmeasured factors may have affected the results.

5 | CONCLUSIONS

The present study showed no significant association between sugammadex and perioperative anaphylaxis in pediatric patients who underwent general anesthesia.

CONFLICT OF INTEREST

The authors report no conflict of interest.

AUTHOR CONTRIBUTION

F.T. wrote the first draft of the manuscript. All authors directly participated in the planning, execution, or analysis of the study. H.Y. initiated the study, wrote the study proposal for the ethics committee, and wrote the main part of the final manuscript. All authors read and approved the version submitted and take full responsibility for the manuscript.

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REFERENCES

1. Plaud B, Meretoja O, Hofmockel R, et al. Reversal of rocuronium-induced neuromuscular blockade with sugammadex in pediatric and adult surgical patients. *Anesthesiology*. 2009;110:284-294.
2. Paton F, Paulden M, Chambers D, et al. Sugammadex compared with neostigmine/glycopyrrolate for routine reversal of neuromuscular block: a systematic review and economic evaluation. *Br J Anaesth*. 2010;105:558-567.
3. Won YJ, Lim BG, Lee DK, Kim H, Kong MH, Lee IO. Sugammadex for reversal of rocuronium-induced neuromuscular blockade in pediatric patients: a systematic review and meta-analysis. *Medicine (Baltimore)*. 2016;95:e4678.
4. Tsur A, Kalansky A. Hypersensitivity associated with sugammadex administration: a systematic review. *Anaesthesia*. 2014;69:1251-1257.
5. Asahi Y, Omichi S, Adachi S, Kagamiuchi H, Kotani J. Hypersensitivity reaction probably induced by sugammadex. *Acta Anaesthesiol Taiwan*. 2012;50:183-184.

6. Takazawa T, Tomita Y, Yoshida N, et al. Three suspected cases of sugammadex-induced anaphylactic shock. *BMC Anesthesiol.* 2014;14:92.
7. Takazawa T, Mitsuhashi H, Mertens PM. Sugammadex and rocuronium-induced anaphylaxis. *J Anesth.* 2016;30:290-297.
8. Sadleir PHM, Russell T, Clarke RC, Maycock E, Platt PR. Intraoperative anaphylaxis to sugammadex and a protocol for intradermal skin testing. *Anaesth Intensive Care.* 2014;42:93-96.
9. Jeyadoss J, Kuruppu P, Nanjappa N, Van Wijk R. Sugammadex hypersensitivity—a case of anaphylaxis. *Anaesth Intensive Care.* 2014;42:89-92.
10. Godai K, Hasegawa-Moriyama M, Kuniyoshi T, et al. Three cases of suspected sugammadex-induced hypersensitivity reactions. *Br J Anaesth.* 2012;109:216-218.
11. Yasunaga H, Matsui H, Horiguchi H, Fushimi K, Matsuda S. Clinical epidemiology and health services research using the Diagnosis Procedure Combination database in Japan. *Asian Pac J Dis Manag.* 2013;7:1-2.
12. Yamana H, Moriwaki M, Horiguchi H, Kodan M, Fushimi K, Yasunaga H. Validity of diagnoses, procedures, and laboratory data in Japanese administrative data. *J Epidemiol.* 2017;27:476-482.
13. Simons FER, Arduzzo LRF, Bilò MB, et al. World Allergy Organization Guidelines for the assessment and management of anaphylaxis. *World Allergy Organ J.* 2011;4:13-37.
14. González-Pérez A, Aponte Z, Vidaurre CF, Rodríguez LAG. Anaphylaxis epidemiology in patients with and patients without asthma: a United Kingdom database review. *J Allergy Clin Immunol.* 2010;125:1098-1104.
15. De Queiroz M, Combet S, BéRard J, et al. Latex allergy in children: modalities and prevention. *Pediatr Anesth.* 2009;19:313-319.
16. Dewachter P, Mouton-Faivre C, Hepner DL. Perioperative Anaphylaxis: What Should Be Known? *Curr Allergy Asthma Rep.* 2015;15:21.
17. Lindsted G, Larsen R, Krøigaard M, et al. Transfusion-associated anaphylaxis during anaesthesia and surgery—a retrospective study. *Vox Sang.* 2014;107:158-165.
18. Munro I, Newberne P, Young V, Bär A. Safety assessment of gamma-cyclodextrin. *Regul Toxicol Pharmacol.* 2004;39(suppl 1):S3-S13.
19. Hotta E, Tamagawa-Mineoka R, Masuda K, et al. Anaphylaxis caused by γ -cyclodextrin in sugammadex. *Allergol Int.* 2016;65:356-358.
20. Baldo BA, McDonnell NJ, Pham NH. Drug-specific cyclodextrins with emphasis on sugammadex, the neuromuscular blocker rocuronium and perioperative anaphylaxis: implications for drug allergy: cyclodextrins, sugammadex and drug allergy. *Clin Exp Allergy.* 2011;41:1663-1678.
21. McDonnell NJ, Pavy TJG, Green LK, Platt PR. Sugammadex in the management of rocuronium-induced anaphylaxis. *Br J Anaesth.* 2011;106:199-201.
22. Clark S, Wei W, Rudders SA, Camargo CA. Risk factors for severe anaphylaxis in patients receiving anaphylaxis treatment in US emergency departments and hospitals. *J Allergy Clin Immunol.* 2014;134:1125-1130.
23. Reddy JI, Cooke PJ, van Schalkwyk JM, Hannam JA, Fitzharris P, Mitchell SJ. Anaphylaxis is more common with rocuronium and succinylcholine than with atracurium. *Anesthesiology.* 2015;122:39-45.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

How to cite this article: Tadokoro F, Morita K, Michihata N, Fushimi K, Yasunaga H. Association between sugammadex and anaphylaxis in pediatric patients: A nested case-control study using a national inpatient database. *Pediatr Anesth.* 2018;00:1–6. <https://doi.org/10.1111/pan.13401>

Supplement table 1 Baseline variables of patients in the matched case–control sample
for probable anaphylaxis (anaphylactic shock)

	No sugammadex n=339	Sugammadex n=401	Total n=740	P value
Age (years), n (%)				
< 1	28 (8.3)	22 (5.5)	50 (6.8)	0.059
1 to 5	24 (7.1)	26 (6.5)	50 (6.8)	
6 to 11	112 (33.0)	108 (26.9)	220 (29.7)	
12 to 18	175 (51.6)	245 (61.1)	420 (56.8)	
Fiscal year,				
2010	39 (11.5)	29 (7.2)	68 (9.2)	0.059
2011	45 (13.3)	35 (8.7)	80 (10.8)	
2012	52 (15.3)	68 (17.0)	120 (16.2)	
2013	86 (25.4)	99 (24.7)	185 (25.0)	
2014	62 (18.3)	85 (21.2)	147 (19.9)	
2015	55 (16.2)	85 (21.2)	140 (18.9)	
Male, n (%)	195 (57.5)	240 (59.9)	435 (58.8)	0.549
Academic, n (%)	149 (45.2)	191 (50.3)	340 (47.9)	0.176

Supplement table 2 Baseline variables of patients in the matched case–control sample for probable and possible anaphylaxis (anaphylaxis associated signs/symptoms combined with skin lesions)

	No sugammadex n=1,279	Sugammadex n=1,060	Total n=2,339	P value
Age (years), n (%)				
< 1year	306 (23.9)	179 (16.9)	485 (20.7)	<0.001
1 to 5	267 (20.9)	176 (16.6)	443 (18.9)	
6 to 11	313 (24.5)	268 (25.3)	581 (24.8)	
12 to 18	393 (30.7)	437 (41.2)	830 (35.5)	
Fiscal year,				
2010	166 (13.0)	65 (6.1)	231 (9.9)	<0.001
2011	288 (22.5)	131 (12.4)	419 (17.9)	
2012	221 (17.3)	164 (15.5)	385 (16.5)	
2013	233 (36.4)	245 (46.2)	478 (40.9)	
2014	185 (14.5)	200 (18.9)	385 (16.5)	
2015	186 (14.5)	255 (24.1)	441 (18.9)	
Male, n (%)	721 (56.4)	581 (54.8)	1,302 (55.7)	0.452
Academic, n (%)	683 (53.4)	535 (50.5)	1,218 (52.1)	0.117