Safety of sugammadex for reversal of neuromuscular block: a post-marketing study based on the World Health Organization pharmacovigilance database

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Abstract

Aim: Residual neuromuscular blockade is a common complication after general anaesthesia. Sugammadex can reverse the action of aminosteroid neuromuscular blockers. Our study aimed to explore sugammadex safety issues in the real world and determine the spectrum of adverse reactions. Methods: All sugammadex-related adverse events reported in VigiBase between 2010 and 2019 were classified by group queries according to the Medical Dictionary for Regulatory Activities. A disproportionality analysis of data was performed using the information component (IC); positive IC values were deemed significant. Results: Overall, 16,219,410 adverse events were reported, and 2032 were associated with sugammadex. The most frequent reactions were recurrence of neuromuscular blockade (n = 54, IC: 6.74, 95% credibility interval [CI]: 6.33–7.10), laryngospasm (n = 53, IC: 6.05, IC025:5.64), bronchospasm (n = 119, IC: 5.63 , IC025:5.36), and bradycardia (n = 169, IC: 5.13, IC025:4.90). Fatal cases were more likely with cardiac disorders, especially in patients over 65 years. In addition, the common adverse drug reactions (ADRs) differed between different age groups ($P < 0.01$). The ADRs were higher between 0–17 years than in other age groups. The onset time of common ADRs was typically within one day, and 68.9% occurred within half an hour after sugammadex administration. Conclusions: Anaesthesiologists should carefully monitor the anaesthesia recovery period to correct the adverse drug reactions caused by sugammadex and recommend monitoring neuromuscular function throughout the anaesthesia process. Sugammadex should be used carefully in patients with cardiovascular diseases, and ECG and hemodynamic changes monitored after medication.

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Running title: Sugammadex safety for block reversal

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Keywords

adverse drug reaction, disproportionality analysis, onset time, reversal of neuromuscular block, sugammadex, VigiBase

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What is already known about this subject:

- Previous studies on the safety of sugammadex have mostly been single-centre studies or meta-analyses.
- The WHO global database of individual case safety reports, namely VigiBase, is the largest source of safety issues related to sugammadex in the real world.
- These data were not previously analysed.

What this study adds:

- We analysed the adverse reactions associated with sugammadex in VigiBase.
- Recurrence of neuromuscular blockade and cardiorespiratory issues were the most frequent adverse reactions reported in some lethal cases.
- Patients should be carefully monitored after sugammadex administration, especially at age 0-17 years, $>$ 65 years, or with cardiac diseases.

Abstract

Aim: Residual neuromuscular blockade is a common complication after general anaesthesia. Sugammadex can reverse the action of aminosteroid neuromuscular blockers. Our study aimed to explore sugammadex safety issues in the real world and determine the spectrum of adverse reactions.

Methods: All sugammadex-related adverse events reported in VigiBase between 2010 and 2019 were classified by group queries according to the Medical Dictionary for Regulatory Activities. A disproportionality analysis of data was performed using the information component (IC); positive IC values were deemed significant.

Results: Overall, 16,219,410 adverse events were reported, and 2032 were associated with sugammadex. The most frequent reactions were recurrence of neuromuscular blockade (n = 54, IC: 6.74, IC_{025}: 6.33), laryngospasm (n = 53, IC: 6.05, IC_{025}: 5.64), bronchospasm (n = 119, IC: 5.63 , IC_{025}: 5.36), and bradycardia (n = 169, IC: 5.13, IC_{025}: 4.90). Fatal cases were more likely with cardiac disorders, especially in patients over 65 years of age. In addition, the common adverse drug reactions (ADRs) differed between different age groups ($P < 0.01$). The ADRs were higher between age 0–17 years than in other age groups. The onset time of common ADRs was typically within 1 day, and 68.9% occurred within half an hour after sugammadex administration.

*Conclusions:*Anaesthesiologists should carefully monitor the anaesthesia recovery period to correct the ADRs caused by sugammadex and recommend monitoring neuromuscular function throughout the anaesthesia process. Sugammadex should be used carefully in patients with cardiovascular diseases, and electrocardiography and hemodynamic changes should be monitored after medication.

Introduction

Muscle relaxation is a fundamental element of general anaesthesia. The neuromuscular blockers commonly used to assist general anaesthesia and promote tracheal/mechanical ventilation can provide quality surgical

conditions by reducing muscle tension. However, residual neuromuscular blockade is a common complication after general anaesthesia. A Chinese study[1] reported that the incidence of residual neuromuscular blockade during extubation for anaesthesia resuscitation was approximately 57.8%. Residual neuromuscular blockade may lead to a series of respiratory complications, such as hypoxemia and atelectasis, and cause subjective discomfort to the patient; death may occur in severe cases[2, 3].

Sugammadex is a new type of specific neuromuscular block antagonist. It was first introduced in Europe in 2008[4]; it was approved in the United States in 2015 and China in 2017. Sugammadex is a cyclodextrin derivative that specifically antagonizes non-depolarizing aminosteroid muscle relaxants that contain a hydrophilic outer layer and a lipophilic core. Rocuronium and vecuronium are specifically encapsulated in the lipophilic core, and sugammadex exerts antagonistic effects against them[5]. Compared with the traditional muscle relaxant antagonist, neostigmine, it achieved faster recovery of neuromuscular function[6] (mean time to effect: 3 min) and improved patient safety[7]. Therefore, the muscle relaxants and anaesthesia reversal guidelines[8] issued by the French Society of Anaesthesiology and Critical Care Medicine in 2020 recommend that appropriate doses of sugammadex should be administered according to body weight to antagonize the neuromuscular block during the recovery period from general anaesthesia in patients who have received rocuronium.

However, with the more frequent clinical use of sugammadex, reports of its adverse reactions have recently increased, and safety issues have become more prominent. Previous studies on the safety of sugammadex have mostly been single-centre studies or meta-analyses; this study is based on the World Health Organization (WHO) global database of individual case safety reports, namely VigiBase[9], to explore the safety issues related to sugammadex in the real world. This database can provide data on rare adverse drug reactions (ADRs) and enable adverse reaction mapping of a wide spectrum of events.

Methods

2.1 Data source

We obtained the data from VigiBase, the largest pharmacovigilance worldwide database, maintained by the Uppsala Monitoring Centre (UMC), the WHO Collaborating Centre for International Drug Monitoring. The UMC receives reports of suspected ADRs from national centres in countries participating in the WHO Program for International Drug Monitoring (https://www.who-umc.org/vigibase/vigibase/). VigiBase contains more than 28 million individual case safety reports (ICSRs) from approximately 150 member states since 1968, covering approximately 99% of the world's population. Drugs are coded according to WHODrug, and ADRs according to MedDRA references (version 20.1)[10].

2.2 Study design

This observational and retrospective pharmacovigilance study explored the association between sugammadex and suspicious ADRs through a disproportionality analysis (also known as case/non-case analysis). The reference group included all ADRs in the VigiBase database. If the proportion of ADRs in patients exposed to sugammadex was greater than in patients not exposed to the drug, an association between the drug and ADRs was suspected, a potential safety signal. We analysed the detailed clinical characteristics of ADRs associated with sugammadex in Vigibase to draw a spectrum of possible adverse reactions of this drug, stratify the patients by age, and analyse the similarities and differences between patients in different age groups. The main time window for ADRs after using sugammadex was analysed according to the reaction onset time.

2.3 Statistical analysis

We extracted ICSRs between January 1, 2010 and December 31, 2019, with sugammadex as the "suspect" drug, excluding repetitive reports. The information component (IC) was used to detect and quantify the association between the target drug and suspected ADRs. Originating from Bayesian confidence propagation neural networks, IC can provide a conservative correlation measure and reduce the risk of highlighting spurious associations, especially for events with very low expected frequencies in large databases (such

as VigiBase)[11]. IC and the corresponding lower end of the 95% credibility interval (IC_{025}) were used to calculate the disproportionality. These parameters compare the proportions of ICSRs of a selected ADR between patients exposed and not exposed to the target drug. If the proportion in the exposed patients is significantly higher than in the control group, a signal is detected. An $IC_{025} > 0$ is the criterion for generating a signal. A positive IC_{025} value is the traditionally used statistical significance threshold for UMC signal detection, indicating that a particular drug-ADR combination has a higher frequency than expected; thus, the ADR has a potential association with the drug[12]. A signal with a higher IC value indicates a strong association between ADR and the drug. An IC value > 3 is defined as a strong signal[13]. The statistical formula to calculate IC[14] is as follows:

$IC = \log_2[(A + 0.5)/(N_{expected} + 0.5)]$

$N_{expected} = (A + B) \times (A + C)/(A + B + C + D)$

$IC_{025} = IC - 3.3 \times (A + 0.5)^{-1/2} - 2 \times (A + 0.5)^{-3/2}$

$IC_{975} = IC + 2.4 \times (A + 0.5)^{-1/2} - 0.5 \times (A + 0.5)^{-3/2}$,

where A is the number of target ADRs in patients using the target drug, B is the number of other ADRs in patients using the target drug, C is the number of target ADR in patients using other drugs, D is the number of other ADRs in patients using other drugs, and $N_{expected}$ is the number of case reports expected for the drug-adverse effect combination. A, B, C, and D were obtained as the frequencies of ICSRs calculated from VigiBase.

Results

Descriptive analysis

A total of 16,219,410 adverse events were reported by patients receiving any drug treatment and included in VigiBase between January 1, 2010 and December 31, 2019. After data deduplication and pre-processing, a total of 2,032 patients with ADRs and sugammadex as the suspected drug were identified. A summary of the demographic data is presented in Table 1.

Comprehensive spectrum of sugammadex-related ADRs

The disproportionality analysis of ADR reports in the full database revealed a total of 94 sugammadex-related positive signals (Fig. 1). They mainly involved the system organ classes (SOCs) of respiratory, thoracic, and mediastinal disorders; cardiac disorders; injury; poisoning and procedural complications; and investigations. A high signal intensity was noted for the recurrence of neuromuscular blockade (n = 54, IC: 6.74, IC_{025}: 6.33), laryngospasm (n = 53, IC: 6.05, IC_{025}: 5.64), bronchospasm (n = 119, IC: 5.63, IC_{025}: 5.36), and bradycardia (n = 169, IC: 5.13, IC_{025}: 4.90).

Relationship between the sugammadex-related ADRs and patient age

The ICSR patients were divided into age-based groups (0–17 years, 18–44 years, 45–64 years, and [?] 65 years), and an IC analysis was performed for each age group. The IC_{025} value was obtained for each group (Figs. 2 and 3); the ANOVA test showed statistically significant differences between groups ($P < 0.01$) with the highest overall signal intensity in the 0–17 years group. The ADRs most commonly reported by different age groups were dissimilar. In the 0–17 years group: prolonged therapeutic effect (n = 1, IC: 18.00, IC_{025}: 14.22), fixed pupils (n = 1, IC: 16.42, IC_{025}: 12.63), and negative-pressure pulmonary oedema (n = 1, IC: 16.29, IC_{025}: 12.50); 18–44 years group: recurrence of neuromuscular blockade (n = 3, IC: 12.16, IC_{025}: 10.09), alveolar-arterial oxygen gradient increased (n = 1, IC: 13.53, IC_{025}: 9.74), and negative-pressure pulmonary oedema (n = 1, IC: 11.94, IC_{025}: 8.16); 45–64 years group: recurrence of neuromuscular blockade (n = 11, IC: 12.44, IC_{025}: 11.41), post-resuscitation encephalopathy (n = 1, IC: 13.41, IC_{025}: 9.62), and increased airway peak pressure (n = 4, IC: 10.47, IC_{025}: 8.70); [?] 65 years group: recurrence of neuromuscular blockade (n = 9, IC: 12.29, IC_{025}: 11.13), increased airway peak pressure (n = 2, IC: 10.45, IC_{025}: 7.87), and prolonged neuromuscular block (n = 3, IC: 9.24, IC_{025}: 7.17).

Onset time of sugammadex-related ADRs

The time to onset is the time from the start of medication administration to an ADR. A total of 1,118 sugammadex-related ADRs were reported with onset time in the database and 1,996 total ADRs. Among these, 68.9% (n = 1376) occurred within half an hour, 88.3% (n = 1763) within 1 day, and < 3% after 7 days. ADRs with significant positive signals, such as the recurrence of neuromuscular blockade, laryngospasm, and bronchospasm, mainly occurred within 1 day after the administration.

Seriousness of sugammadex-related ADRs

One patient may correspond to more than one ADR, resulting in more than one outcome, and there are a total of 3717 outcomes of 2032 patients. Among the 3717 ADR outcomes reported, 53 were fatal; the most frequent fatal ADR was death (9/53, 17.0%), and the SOC with the most frequent fatal cases was cardiac disorders (21/53, 39.6%). All the fatal ADRs occurred in 27 patients, 1.33% of sugammadex-related ICSRs; the majority of these patients were over 65 years of age (12/27, 44.4%), and the number of men and women was similar.

Discussion

To our knowledge, this study is the most extensive safety analysis of sugammadex in recent years, reporting the characteristics of adverse reactions associated with sugammadex through a detailed analysis of the WHO Global Case-safety Reporting Database (VigiBase).

We found 94 positive signals of adverse reactions related to sugammadex through the disproportionality analysis, mainly involving the respiratory, cardiovascular, and immune systems. The four ADRs with the highest signal intensity for sugammadex association were the recurrence of neuromuscular blockade, laryngospasm, bronchospasm, and bradycardia. An online app-based study[15] in 2018 showed that the most common ADRs of sugammadex were bradycardia and incomplete neuromuscular blockade reversal, similar to our findings.

The majority (68.9%) of ADRs occurred within half an hour from sugammadex administration, suggesting that the patients should be monitored carefully to detect any adverse reactions during the anaesthesia recovery period. Nemes et al.[16] found that the incidence of residual postoperative neuromuscular block after reversal with sugammadex was significantly lower than with neostigmine or placebo; however, it could still not be avoided entirely. Errando et al.[17] reported that women have a higher incidence of residual postoperative neuromuscular block than men; furthermore, a residual block cannot be completely avoided without neuromuscular monitoring, regardless of the antagonism strategy. Therefore, we recommend neuromuscular function monitoring throughout anaesthesia and that the reversal of muscle relaxation should always be driven by the monitored data. Appropriate reversals in terms of medication, dose, and timing should never blindly follow established rules.

We found that sugammadex-related ADRs have the highest fatality rate involving cardiac disorders. At the same time, cardiac disorders are also the SOC with the highest frequency of ADRs in association with sugammadex. Several cases[18-21] of severe bradycardia and cardiac arrest have been reported clinically, and Hunter et al.[22] found that since 2016, the number of serious adverse cardiac events reported after sugammadex in the Food and Drug Administration (FDA) Adverse Event Reporting System has greatly exceeded that after neostigmine. At present, the exact mechanism of sugammadex-induced bradycardia and asystole is still unclear; however, Kalkan et al. found that both low and high doses of sugammadex can cause significant histopathological changes in cardiomyocytes and other harmful effects. Nonetheless, this finding suggests that anaesthesiologists should use sugammadex cautiously in patients with underlying cardiovascular diseases during clinical medication. They should also conduct comprehensive electrocardiography (ECG) and hemodynamic change monitoring after the medication.

We stratified the reports of adverse events by age and found that patients aged 0–17 years were the group with the highest risk of ADRs due to saccharides. However, in contrast to our findings, Gaver et al.[23] reported that sugammadex was as effective and safe in the paediatric population (age < 19 years) as in adults, whereas Honing et al.[24] showed that elderly patients were more susceptible to the adverse effects

of residual neuromuscular blockade and had a slower natural recovery. In addition, it is worth noting that pupil fixation, a common drug toxicity reaction, had a strong positive signal in the paediatric group, though not in the entire database, and we suspect that this finding may be related to renal immaturity and delayed drug metabolism in children. However, there were some cases where the number of ADR was less than three in the age-stratified disproportionate analysis, suggesting that the analysis of the adverse reactions of sugammadex in different age groups requires a larger amount of data. Currently, sugammadex has not been approved by the FDA for use in children. There are limited data on the use of sugammadex in children, especially infants. Further paediatric studies are required to fully determine the safety of sugammadex in children. We acknowledge that the VigiBase database has some limitations. Incomplete reports of ADRs and lack of complete clinical information are common limitations of pharmacovigilance studies. First, adverse event reporting is voluntary and performed by various sources (e.g., doctors, pharmacists, and other clinicians), thus increasing the risk of incomplete information. However, 130 countries have contributed to the database, thus ensuring a comprehensive assessment from different clinical settings. Second, no detailed clinical information and diagnostic criteria were available; thus, our assessment was limited to reports from treating clinicians, which may be subject to various biases, including underreporting (reporting only the most severe or obvious cases) or overreporting (reporting cases without a clear diagnosis). Inevitably, reporting of adverse events is more likely soon after the launch of a new drug than during regular, long-standing use. In addition, it is important to note that when conducting ADR studies, the IC value does not indicate a causal relationship between the target drug and the suspected ADRs; it only shows a quantitative association[13]. Therefore, prospective studies and long-term validation of these findings are required. Despite the limitations of VigiBase, the analysis of adverse reactions in the pharmacovigilance database remains an important tool for drug safety studies and post-marketing drug monitoring. It allows for signal detection in large populations and can provide significant opportunities for monitoring drug safety and identifying new, rare signals.

In conclusion, research based on spontaneous ADR reporting is an important modality for drug safety research and post-marketing drug monitoring. In the safety profile of sugammadex, our result was similar to that of the post-marketing clinical trials. We found that adverse effects of sugammadex were at higher risk in adolescents and more severe in older patients, for which further research should be performed. In addition, our findings highlight important concerns about the time onset of adverse events and cardiac safety, and we suggest that anesthesiologists should carefully monitor the anesthesia recovery period, especially for ECG and hemodynamic changes in patients with underlying cardiovascular diseases.

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Declaration of interests

The authors declare that they have no conflict of interest.

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Tables

Table 1. Clinical characteristics of patients with sugammadex-related adverse reactions in the database

		n (%)
Sex	Sex	
	Male	892 (43.90)
	Female	894 (44.00)
	Unknown	246 (12.11)
Age (years)	Age (years)	
	0-17	132 (6.50)
	18-44	363 (17.86)
	45-64	534 (26.28)
	[?] 65	469 (23.08)
	Unknown	534 (26.28)
Year	Year	
	2010	21 (1.03)
	2011	21 (1.03)
	2012	44 (2.17)
	2013	153 (7.53)
	2014	110 (5.41)
	2015	145 (7.14)
	2016	310 (15.26)
	2017	372 (18.31)
	2018	361 (17.77)
	2019	495 (24.36)
Region	Region	
	Africa	18 (0.89)
	Americas	439 (21.60)
	Asia	968 (47.64)
	Europe	471 (23.18)
	Oceania	136 (6.69)
Outcome[a]	Outcome[a]	
	Fatal	53 (1.43)
	Not recovered/not resolved	50 (1.35)
	Recovered/resolved	2283 (61.41)
	Recovered/resolved with sequelae	17 (0.46)
	Recovering/resolving	239 (6.43)

	n (%)
Unknown	1075 (28.93)

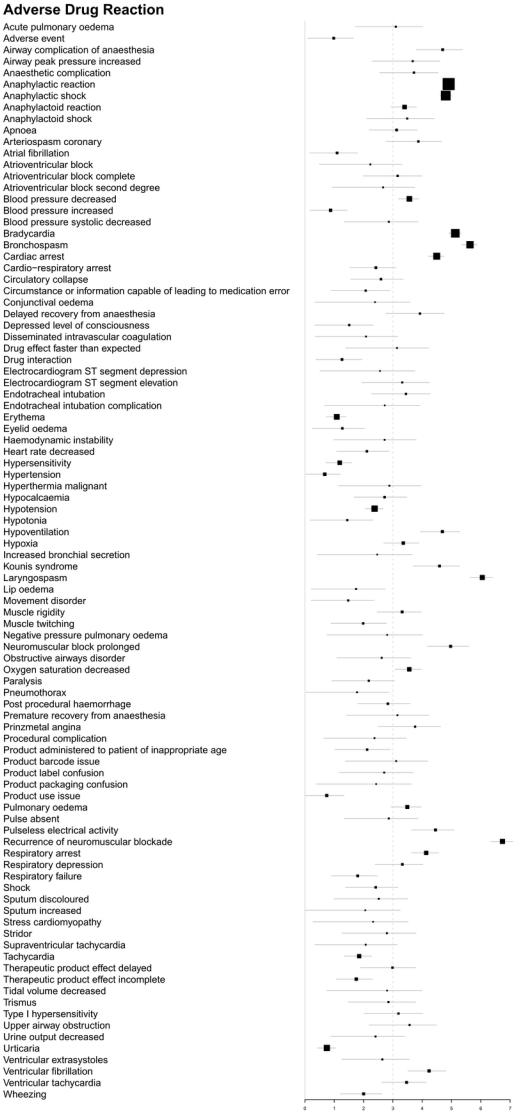
[a]In total, 3717 outcomes were reported in 2032 patients.

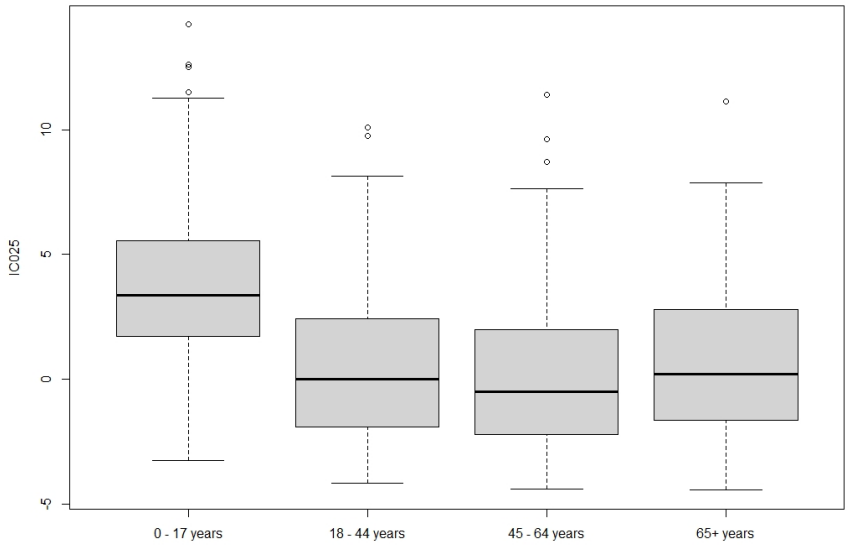
Figure legends

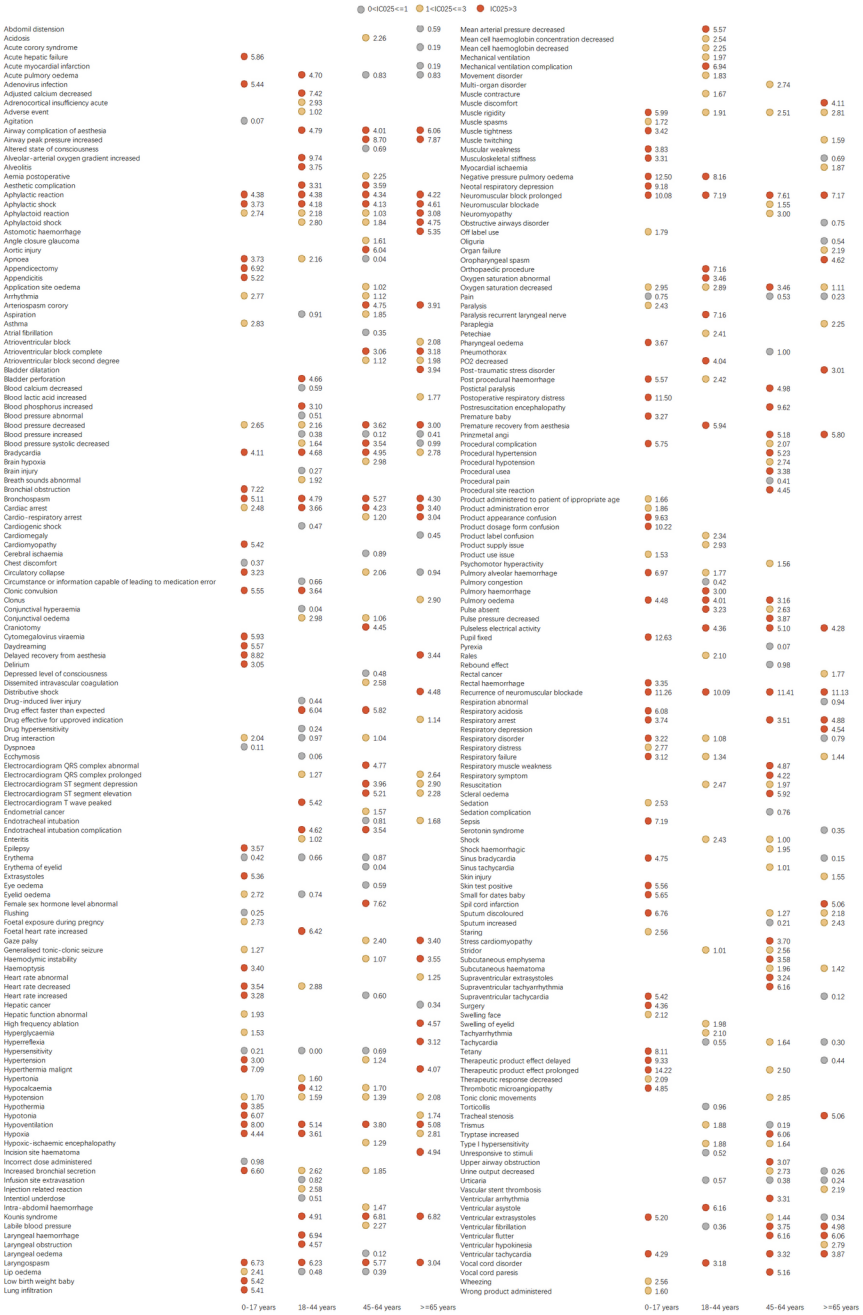
Fig. 1. Comprehensive spectrum of adverse reactions related to sugammadex reported by VigiBase with positive results from the disproportionate analysis. $IC_{025} > 3$ was considered a significant association signal, indicating that the adverse reactions have a strong correlation with sugammadex use.

Fig. 2. Results of the analysis of variance of IC_{025}values of adverse drug reactions in each age group. The ANOVA test showed statistically significant differences ($P < 0.01$) between age groups, indicating that the overall intensity of adverse reaction signals in the 0–17 years group was the highest.

Fig. 3. Spectrum of adverse drug reactions (ADRs) in different age groups. No signal means no related ADR in this age group or ADR with $IC_{025} < 0$.







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