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Risk of bronchospasm and coronary arteriospasm with sugammadex use: a post marketing analysis

Pushkar Aggarwal

Abstract

Introduction: Sugammadex is used for the reversal of neuromuscular blockade caused by rocuronium bromide and vecuronium bromide. As part of the post licensing phase of drug development, adverse events related to the use of sugammadex are still being uncovered and being reported. The potential association between sugammadex and adverse events bronchospasm and coronary arteriospasm using a retrospective pharmacovigilance signal analysis was carried out.

Methods: Food and Drug Administration's Adverse Event Reporting System database was used to run disproportionality analyses to investigate the potential association of sugammadex with bronchospasm or coronary arteriospasm. In this analysis we report the adverse event signal using frequentist methods of Relative reporting ratio (RRR), proportional reporting ratio (PRR), reporting odds ratio (ROR) and the Bayesian based Information Component metric.

Results: A statistically significant disproportionality signal is found between sugammadex and bronchospasm ($n = 44$; chi-squared = 2993.87; PRR = 71.95 [95% CI: 54.00–95.85]) and sugammadex and coronary arteriospasm ($n = 6$; chi-squared = 209.39; PRR = 43.82 [95% CI: 19.73–97.33]) as per Evans criteria. Both statistically significant disproportionality signals persisted when stratified by gender. Based upon dynamic cumulative PRR graph, the PRR value has steadily increased and the 95% CI narrowed since December 2012.

Conclusion: The results of the pharmacovigilance analysis highlight a statistically significant disproportionality signal between sugammadex usage and bronchospasm and coronary arteriospasm adverse events. Physicians need to be aware of these adverse events when using sugammadex. The results of the pharmacovigilance signal analysis highlight a statistically significant disproportionality signal between sugammadex usage and bronchospasm and coronary arteriospasm adverse events. Physicians need to be aware of these adverse events when using sugammadex.

Keywords: Sugammadex, Bronchospasm, Coronary Arteriospasm

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Introduction

Neuromuscular blocking agents (NMBA) are often given in conjunction with anesthesia during surgical procedures to facilitate endotracheal intubation and inhibit spontaneous ventilation. Use of NMBA during intubation can decrease the chances of damage to the vocal cords and facilitate mechanical ventilation in patients with decreased lung compliance.[1,2] Sometimes, during or after procedures, there is a need to reverse the neuromuscular blocking agent. Specifically, the risk of residual neuromuscular blockade can

Correspondence to:
Pushkar Aggarwal
University of Cincinnati College of Medicine, 2545 Dennis Street Apt 7105, Cincinnati, Ohio, USA
aggarwpr@mail.uc.edu

necessitate the need for a NMBA reversal drug.[3] One of the oldest and most commonly used NMBA reversal drugs is neostigmine. Neostigmine was patented in 1931 and the World Health Organization includes it in the list of medications considered to be the most efficacious and safe: "WHO Model List of Essential Medicines".[4] Until late 2015, neostigmine and other acetylcholinesterase inhibitors were the primary treatment option for NBMA reversal in the U.S. On December 15, 2015, sugammadex was approved by the Food and Drug Administration (FDA) for the reversal of neuromuscular blockade caused by rocuronium bromide and vecuronium bromide.[5] However, worldwide, sugammadex has been clinically used for several years, including in the European Union from July 2008 and subsequently in Japan from April 2010.

As part of the post licensing phase of drug development, adverse events related to the use of sugammadex are still being uncovered and being reported. As of September 3, 2018, the FDA was evaluating the need for regulatory action regarding a link between sugammadex use and bronchospasm and between sugammadex use and laryngospasm.[6] Bronchospasm is a condition in which there is a sudden involuntary contraction of muscle in the bronchiole. It can result in difficulty in breathing, desaturation and, in some cases, death.[7,8] In addition, in 2014, the Pharmaceuticals and Medical Devices Agency of Japan recommended adding "coronary arteriospasm" in the clinically significant adverse reactions section of sugammadex's drug label in Japan.[9,10] Coronary arteriospasm results in decreased blood flow to the muscle of the heart and can result in myocardial infarction.

Objective

This research paper quantifies the signal between sugammadex and adverse events bronchospasm and coronary arteriospasm using a retrospective pharmacovigilance signal analysis. Specifically, a disproportionality analysis is conducted to determine if the signal score is significant. A disproportionality analysis can be used to identify potential statistical associations between a product and an event based on safety/case reports. The analysis is performed on the FDA Adverse Event Reporting System (FAERS),[11] a passive reporting system, which does not provide information about the prior medical history of the patient. Further, the pharmacovigilance signal analysis, by itself, does not demonstrate causal associations. However, FAERS has advantages in identifying drug-safety signals in real-world situations. In addition, case reports from literature are summarized and used to support or contradict the analysis.

Methods

Approval by institutional review board or human subjects' committee was not required as the analysis was of retrospective public domain safety data that was without any personal identifiers.

The FDA maintains and manages the FDA Adverse Event Reporting System. Case reports of adverse events for FAERS are submitted by healthcare professionals, consumers, and manufacturers. FAERS allows users to explore reports of adverse events that may occur in potential association with use of drug products, singularly or in combination with other drugs. FAERS is updated quarterly.[11] FAERS data from January 1, 2004 to June 30, 2018 was accessed and used for this analysis. The FAERS data was searched for adverse event case reports in which sugammadex was listed as a drug administered and bronchospasm or coronary arteriospasm was reported as an adverse event, respectively for each of the two adverse event disproportionality analyses. Efforts were made to remove duplicate case reports prior to running the analysis.

Disproportionality analysis in drug safety research can be used to identify signals and potential statistical associations between a product and an event based on databases of safety/case reports.[12,13] The analysis compares the reported expected count for a product-event combination with the reported observed count. High reporting ratios indicate that disproportionality exists and that there may be a potential statistical association between the product and the adverse event.[14,15] Relative reporting ratio (RRR), proportional reporting ratio (PRR), reporting odds ratio (ROR) and chi squared with Yates' correction are calculated in the disproportionality analysis. The PRR is the rate of reporting of one specific event among all events for a given drug, the comparator being this reporting rate for all drugs present in the database, including the drug of interest. The ROR is the ratio of the odds of reporting of one specific event *versus* all other events for a given drug compared to this reporting odds for all other

drugs present in the database.[16] The RRR compares the probability of reporting one specific event by a given drug to the probability of reporting the same specific event by all drugs.

Other disproportionality measures which can be used to decipher a signal are information component (IC) and the empirical Bayes geometric mean (EBGM). These algorithms, however, differ from the above disproportionality algorithms in that the PRR, RRR and ROR utilize a frequentist approach, whereas the IC and EBGM utilize a Bayesian approach.[17,18] The PRR is currently used by the UK Medicines and Healthcare products Regulatory Agency (MHRA), the ROR by the Netherlands Pharmacovigilance Centre, the IC by the World Health Organization (WHO), and the EBGM by the FDA.[18] For large sample sizes, as in FAERS database, the score that each of these statistics produces for any given drug-event combination is likely to be similar. FDA implemented Multi-item Gamma Poisson Shrinker (MGPS) data mining algorithm to calculate EBGM values, which are the ratios of the observed to the expected number of drug-event pairs (reporting ratios). MGPS allows the use of stratification for elimination of some confounding effects, so it will typically provide lower scores if there is a confounding variable involved, such as age or gender, compared to a statistic that does not involve stratification. However, randomized trials are the only way of being sure there is no confounding in a dataset. Moreover, Bayesian Confidence Propagation Neural Network (BCPNN) analysis was proposed based on Bayesian logic where the relation between the prior and posterior probability was expressed as the information component. The IC given by the BCPNN is applied by the WHO Uppsala Monitoring Center (UMC).

Signal detection using IC is done using the IC025 metric, a criterion indicating the lower bound of the 95% two-sided confidence interval of the IC, and a signal is detected if the IC025 value exceeds zero.[19] Evans *et al.* define a criterion by which to evaluate whether the disproportionality analysis indicates a statistically significant signal or not: a PRR greater than or equal to 2, chi-squared greater than or equal to 4 and number of events greater than or equal to 3.[15] In addition, according to Van Puijenbroek *et al.*, a lower 95% CI of ROR greater than 1 indicates a statistically significant signal between a drug and an event.[20] In this analysis we report the adverse event signal using frequentist methods of RRR, ROR and PRR and the Bayesian based IC025 metric.

Results

The FAERS database (January 1, 2004 to June 30, 2018) contained over 9 million worldwide adverse event reports as associated with any drug. In the database, an adverse event was reported with sugammadex use in 698 case reports. 44 and 6 cases of bronchospasm and coronary arteriospasm, respectively, were reported as associated with sugammadex as the suspect drug.

2×2 contingency tables were constructed to calculate the PRR, RRR and ROR along with their 95% confidence intervals, the chi-squared with Yates correction and the information component metrics. All of these disproportionality values are shown in Tables 1 and 2. When using the information component criteria (IC lower 95% CI > 0), a signal is detected for sugammadex with bronchospasm (IC lower 95% CI = 4.82) and sugammadex with coronary arteriospasm (IC lower 95% CI = 1.94) (Table 1). When comparing the results of the disproportionality analysis of sugammadex associated bronchospasm ($n = 44$; chi-squared = 2993.87; PRR = 71.95 [95% CI: 54.00–95.85]) to Evans criteria ($n >= 3$; chi-squared $>= 4$; PRR $>= 2$), sugammadex is found to contain a statistically significantly disproportionally signal with bronchospasm. Similarly, the disproportionality results of sugammadex associated coronary arteriospasm ($n = 6$; chi-squared = 209.39; PRR = 43.82 [95% CI: 19.73–97.33]) are statistically significant as per Evans criteria. When using Van Puijenbroek's criteria (ROR Lower 95% CI > 1), sugammadex associated bronchospasm (ROR lower 95% CI = 56.49), and sugammadex associated coronary arteriospasm (ROR lower 95% CI = 19.76) are found to be statistically significant (Table 2).

The data was also stratified by gender and by age for case reports with sugammadex and bronchospasm. The disproportionality analysis results are also displayed in Tables 1 and 2. The results show that the signal of bronchospasm was statistically significantly associated with sugammadex use for males and for females and for the age groups using Evan's criteria and Van Puijenbroek's criteria. Coronary arteriospasm was statistically

Table 1. Information component value and information component lower 95% CI for the potential association between bronchospasm and coronary arteriospasm adverse events and sugammadex between 1 January 2004 and 30 June 2018 as a total and stratified by gender and by age group.

	Stratification	Information component value	IC_{025}
Bronchospasm	Total	5.32	4.82
	Male	4.36	3.49
	Female	4.95	4.25
	0–40 years old	3.31	1.90
	41–60 years old	3.90	2.76
	61–80 years old	3.50	2.20
Coronary Arteriospasm	Total	3.35	1.94
	Male	2.62	0.55
	Female	2.67	0.60

Table 2. Proportional reporting ratio (PRR), reporting odds ratio (ROR), relative reporting ratio (RRR) and chi-squared with Yates correction for the potential association between bronchospasm and coronary arteriospasm adverse events and sugammadex between 1 January 2004 and 30 June 2018 as a total and stratified by gender and by age group.

	Stratification	Analysis	Value	Lower 95% CI	Upper 95% CI
Bronchospasm	Total	PRR	71.95	54.00	95.85
		ROR	76.72	56.49	104.19
		RRR	71.56	53.71	95.33
		Chi-squared with Yates correction	2993.87	–	–
	Male	PRR	59.33	36.21	97.21
		ROR	62.62	37.18	105.49
		RRR	59.03	36.03	96.72
		Chi-squared with Yates correction	799.45	–	–
	Female	PRR	89.17	60.19	132.12
		ROR	96.83	63.17	148.41
		RRR	88.73	59.89	131.46
		Chi-squared with Yates correction	1910.11	–	–
	0–40 years old	PRR	38.95	17.85	85.00
		ROR	41.08	18.02	93.64
		RRR	38.79	17.77	84.65
		Chi-squared with Yates correction	184.98	–	–

(Continued)

Table 2. (Continued)

	Stratification	Analysis	Value	Lower 95% CI	Upper 95% CI
	41–60 years old	PRR	66.17	35.23	124.27
		ROR	71.45	36.16	141.19
		RRR	65.80	35.04	123.58
		Chi-squared with Yates correction	512.02	–	–
	61–80 years old	PRR	43.42	21.03	89.63
		ROR	45.51	21.27	97.35
		RRR	43.23	20.94	89.25
		Chi-squared with Yates correction	248.40	–	–
Coronary Arteriospasm	Total	PRR	43.82	19.73	97.33
		ROR	44.19	19.76	98.83
		RRR	43.67	19.66	97.01
		Chi-squared with Yates correction	209.39	–	–
	Male	PRR	43.83	14.19	135.39
		ROR	44.30	14.17	138.49
		RRR	43.67	14.14	134.88
		Chi-squared with Yates correction	86.07	–	–
	Female	PRR	59.20	19.17	182.83
		ROR	59.81	19.14	186.92
		RRR	59.01	19.11	182.23
		Chi-squared with Yates correction	118.01	–	–

significantly associated with sugammadex use for males and for females using Evan's criteria and Van Puijenbroek's criteria. Coronary arteriospasm associated with sugammadex case reports was not stratified by age group due to the limited number of case reports.

To investigate how the PRR has changed over time, a dynamic cumulative PRR graph (December 2012 to June 2018) was constructed for sugammadex and bronchospasm adverse events (Figure 1). December 2012 was chosen as the initial date for the dynamic cumulative PRR because the first case report showing a bronchospasm adverse event after administering sugammadex occurred in the fourth quarter of 2012. Generally, the PRR value has steadily increased and the 95% CI narrowed since December 2012. The dynamic graph for coronary arteriospasm was not generated as the number of cases was low.

Limitations

FAERS is a passive reporting system. Not every adverse event is reported to the database, and therefore, the incidence of an adverse event cannot be calculated.[21] The limitations of FAERS have been documented earlier by FDA.[11] FAERS does not provide information about the prior medical history of the patient nor any risk factors they have. These data and the analysis do not, by themselves, demonstrate causal associations. The

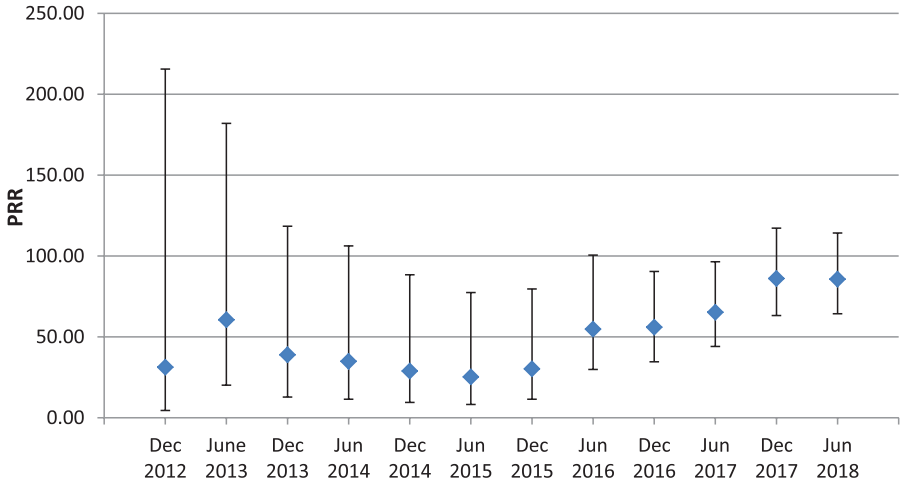

Figure 1. Dynamic cumulative proportional reporting ratio (PRR) of sugammadex and bronchospasm events since December 2012.

event could occur as a result of the underlying disease or diseases and the concomitant drugs or their interaction thereof. Randomized controlled studies are needed in order to establish causality. However, FAERS has advantages in that it can and has been used to identify drug-safety signals, drug-drug interaction and idiosyncratic adverse drug-reactions.[22]

FAERS has advantages in identifying signals in real-world situations, which is near impossible with the limited number of subjects used in the randomized clinical trials. Further, FAERS can help in identifying global differences in occurrence of adverse events.

Discussion

Overview

Sugammadex works by binding to rocuronium or vecuronium in the plasma. This binding leads to a lower concentration of rocuronium/vecuronium in the plasma and, as such, rocuronium/vecuronium exit the neuromuscular junction due to the concentration gradient and enter the plasma. The new rocuronium/vecuronium in the plasma binds to the available sugammadex leading to a decrease in free rocuronium/vecuronium and a subsequent decrease in neuromuscular blocking.[23,24]

19 cases of sugammadex induced bronchospasm or laryngospasm were found in 8 unique case reports when searching PubMed for published case reports that contained the terms sugammadex and bronchospasm or laryngospasm published between January 2010 and August 2018. Two cases had patients with a prior history of asthma while four cases stated that the patients had not been diagnosed with any pulmonary disease. In addition, the other 13 cases did not mention any prior respiratory issues in the patients.

Airway obstruction

A phase III, randomized, 9 hospital site, parallel-group, comparative, safety-assessor blinded study was sponsored/performed by the manufacturer of sugammadex to examine a link between sugammadex and bronchoconstriction.[25] Seventy seven patients with preexisting pulmonary disease who had to undergo surgery and required neuromuscular blockade were included in the study. Two patients, who had history of asthma, received 4 mg/kg sugammadex and were given desflurane for maintenance of anesthesia, developed bronchospasms. However, Eskander *et al.* reported three patients, who did not have prior pulmonary diseases, developed bronchospasm after sugammadex administration.[26] In addition, Lee *et al.* reported a patient who had good cardio-respiratory functional capacity and developed laryngospasm after sugammadex administration.[27] These cases indicate that a positive pulmonary history may not be the sole cause of the bronchospasm/laryngospasm after sugammadex administration.

Mcguire and Dalton reported eight cases in which upper airway obstruction occurred after administration of sugammadex.[28] After seeing a similar airway obstruction in the first three cases, they made variations in the anesthetic drugs administered to the patients to account for a confounding drug. For example, fentanyl was given instead of remifentanil in one patient and sevoflurane was used for maintenance of anesthesia in one patient instead of desflurane. However, all patients who received sugammadex had a subsequent upper airway obstruction. One patient was given neostigmine instead of sugammadex and this patient did not have upper airway obstruction. There are ethical questions regarding the protocol followed by the authors and whether a sufficient maintenance anesthesia depth was used.[29]

Rocuronium-sugammadex complex

In the 77 patient study described above[25] one of the two patients who developed bronchospasms had bronchospasms occur about 1 h after sugammadex administration. The delayed adverse event may be due to the chelation of rocuronium or the sugammadex-rocuronium complex rather than directly due to sugammadex. Okuno *et al.* suggest in a case report that coronary vasospasm induced by anaphylactic shock in a 46 year old may be caused by the rocuronium-sugammadex complex.[30]

Coronary arteriospasm

During the time period 2011–2014, four cases were reported in Japan of sugammadex associated coronary arteriospasm. In all four cases, a causal relationship could not be ruled out and no fatalities were reported.[10] A 76 year old man, with no notable medical history, had repetitive cardiac arrests after administration of sugammadex after prostatectomy.[31] The authors identified the administration of sugammadex as a more probable cause of the coronary spasm. Hoshino *et al.* also reported repetitive cardiac arrests due to coronary vasospasm after sugammadex administration in a 58 year old man and recommended that clinicians should consider sugammadex as one of the causative agents of cardiac arrest in the operating room.[32]

The mechanism by which the spasms are occurring after sugammadex administration is still being understood. However, case reports and the clinical trial suggest that there is a signal between sugammadex usage and bronchospasm and coronary arteriospasm/vasospasm.

Conclusion

The results of the pharmacovigilance signal analysis highlight a significant disproportionality signal between sugammadex usage and bronchospasm and coronary arteriospasm adverse events. The significance of the signals persisted after stratifying the data by gender and by age. The case reports and limited controlled studies support this signal between the drug and the adverse events. Bronchospasm and coronary arteriospasm are serious adverse events that can result in mortality. Physicians need to be aware of these adverse events when using sugammadex. Further studies should be performed to better understand the mechanism by which these adverse events are occurring after sugammadex administration.

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Conflict of interest statement

The author declares that there is no conflict of interest.

ORCID iD

Pushkar Aggarwal https://orcid.org/0000-0001-5271-8127

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