Knowledge and Understanding of the Safety and Efficacy Aspects of BRIDION® Among Canadian Anesthesiologists

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Abstract

Background BRIDION® (sugammadex sodium) is an agent for the reversal of neuromuscular blockade (NMB) induced by rocuronium and vecuronium in general anesthesia. Following the approval of sugammadex in Canada (February 2016), Health Canada required a survey to assess the knowledge and understanding of the safety and efficacy aspects of sugammadex among anesthesiologists in Canada.

Objective Our objective was to evaluate how well the anesthesiologists in Canada understood the safety and efficacy aspects of sugammadex.

Methods A survey was implemented among anesthesiologists in Canada via internet/phone. The survey was organized to test the knowledge of anesthesiologists by utilizing 11 key questions regarding the safety and efficacy of sugammadex. Five additional safety questions that were not considered part of the key messages but were important concepts for anesthesiologists to know when administering sugammadex were also included.

Results A total of 202 completed surveys were collected. Based on an a priori threshold of understanding of 75%, 9 out of 11 key messages scored at or above this threshold. The two messages that scored below this threshold involved (1) knowledge that sugammadex is not indicated for use in children aged < 18 years (71.8%; 95% confidence interval [CI] 65.0–77.9) and (2) that monitoring is required for recurrence of NMB after reversal with sugammadex (73.3%; 95% CI 66.6–79.2). Of the five additional safety questions, four had an understanding rate of ≥ 88.1%. One question scored 60.4%; this question covered the concept that sugammadex is not recommended for use in patients with severe renal impairment (creatinine clearance < 30 mL/min), including those requiring dialysis.

Conclusion In general, the survey results suggested that anesthesiologists understood the use, safety, and efficacy of sugammadex for the reversal of moderate to deep NMB induced by rocuronium or vecuronium in adults undergoing surgery.

1 Introduction

BRIDION® (sugammadex sodium) is an agent used for the reversal of neuromuscular blockade (NMB) induced by rocuronium and vecuronium in general anesthesia. The market authorization holder for sugammadex is Merck & Co. Inc., Kenilworth, NJ, USA. After intravenous injection, sugammadex distributes through the plasma and binds to the neuromuscular blocking agents rocuronium or vecuronium to

form a complex, thus inactivating them. Following approval of sugammadex in Canada (February 2016), Health Canada required a survey to assess the knowledge and understanding (KAU) of the safety and efficacy aspects of sugammadex among anesthesiologists in Canada. Therefore, this survey was implemented to address this regulatory request.

2 Methods

2.1 Survey Sample

The survey sampling frame was identified from a database maintained by Merck, the manufacturer of sugammadex. Merck updates and maintains a database of healthcare professionals (including anesthesiologists) interacted with over time (e.g., in the context of engagement activities, medical education, etc.), and this database complies with

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Key points

This survey demonstrates that Canadian anesthesiologists in general have a good understanding of the use and the safety and efficacy aspects of sugammadex.

Two key messages that were not correctly understood by more than 75% anesthesiologists were related to the lack of the indication for use in children and the need for monitoring of neuromuscular blockade after administration of sugammadex

all applicable privacy guidelines. Participants must have been anesthesiologists who met at least one of the following inclusion criteria: (1) previously participated in a Merck-sponsored educational program related to sugammadex; (2) administered sugammadex in the previous 12 months. Merck-sponsored medical educational programs were events that addressed the medical education needs of anesthesiologists, including the safety and efficacy aspects of sugammadex. Prospective participants were excluded if they met at least one of the following exclusion criteria: (1) had immediate family members who had ever worked for Merck Canada Inc. or any of its affiliates or Health Canada or United BioSource LLC (UBC, the vendor that conducted this survey on behalf of Merck) or (2) did not fulfill either of the inclusion criteria.

The target sample size for this assessment was at least 200 completed surveys. The size of the sample was determined based on both practical and statistical considerations because the population of anesthesiologists was assumed to be limited. Since this was a descriptive study without hypothesis testing, the precision was represented by the width of the confidence interval (CI) around the fractions observed. Based on the width of the exact binomial two-sided 95% CI, at the desired threshold of 75% understanding, the exact binomial two-sided 95% CI is 75% (68.4–80.8).

2.2 Survey Design

The survey was designed to assess each participant's understanding of the important information as presented in the sugammadex product monograph in Canada and in Merck-sponsored educational programs. The key messages evaluated in this KAU survey were organized around the following two primary objectives. Primary objective 1: to assess how anesthesiologists use sugammadex, on the following key knowledge aspects: (a) sugammadex is indicated for the reversal of NMB induced by rocuronium and vecuronium in adult patients undergoing surgery; (b) sugammadex should not be used to reverse NMB induced by nonsteroidal

neuromuscular blocking agents (NMBAs) such as succinylcholine or benzyliisoquinolinium compounds; and (c) sugammadex is not indicated in children aged < 18 years. Primary objective 2: to evaluate how well anesthesiologists understood the safety and efficacy aspects of sugammadex, on the following key message aspects: (a) delayed onset time or insufficient NMB at retreatment with steroidal NMBA; (b) slow recovery from NMB (drug effect decreased); (c) recurrence of NMB; (d) anesthetic complications; (e) use of sugammadex in adult patients with renal impairment (after retreatment with a steroidal NMBA, onset of NMB maybe delayed); (f) hypersensitivity, including anaphylaxis/anaphylactic shock; (g) bronchospasm in adult patients with a history of pulmonary complications and airway obstruction; and (h) bradycardia.

Five additional survey questions were not considered part of the key objectives but were important concepts for anesthesiologists to know while treating patients with sugammadex, including questions involving knowledge around the use and storage of sugammadex.

2.3 Survey Administration

The recruitment list for survey invitations was compiled using information identified from a database maintained by Merck. All anesthesiologists from the list were invited via postal mail or email to participate in the survey. The survey was self-administered by the respondents via a secure web-based internet or administered via telephone with a trained interviewer. This survey was administered between July 2018 and October 2018 in territories throughout Canada where sugammadex was available. Eligibility of the survey participants was assessed through their responses to screening survey questions. The survey was terminated if respondents did not meet inclusion criteria or met exclusion criteria. The survey was available in English and Canadian French and comprised questions or statements with multiple response choices used to collect the survey data from respondents who chose to participate. The survey was voluntary, and the modality was selected based on the respondent's preference. For those who completed the survey, a financial honorarium was provided to compensate for their time in taking the survey. The honorarium was based on fair market value as allowed by local laws and country regulations.

2.4 Statistical Analysis

Statistical analyses were descriptive with no formal hypothesis testing. Knowledge rates were computed for each question/item of the key objective as the proportion of correct responses out of the total of responses. A knowledge rate of $\geq 75\%$ was considered acceptable for this KAU survey.

Subgroup analyses were performed according to the participant's sex, years of practice, geographic region, reading the sugammadex product monograph for Canada, and participation in Merck-sponsored educational programs related to sugammadex.

Statistical analysis of all data was performed using SAS® statistical software (SAS Institute, Cary, NC, USA) (SAS v9.3).

3 Results

A total of 5232 invitations and 5098 reminder letters were distributed to anesthesiologists in Canada. Of the anesthesiologists invited to participate in the survey, 259 (5.8%) responded to the invitation. A total of 205 (79.2%) were eligible for participation and 202 (98.5%) of them completed the survey. Among the 202 participants, 199 (98.5%) completed the survey using the internet; 103 (51.0%) had attended a Merck-sponsored educational program related to sugammadex, and 188 (93.1%) had administered sugammadex in the past 12 months; 80.2% were male; 85.6% had more than 5 years of practice experience as a practicing clinician; and 58.9% reported having their primary practice setting in teaching hospitals. Over 90.0% of the respondents were from central Canada (54.0%), the west coast (British Columbia; 21.3%), or the Atlantic region (17.8%). About half (55.4%) reported that they read the product monograph for sugammadex, and among them, 70.5% reported that they had read at least most of it.

Among those who had administered sugammadex in the past 12 months, the common scenarios for use were in patients at high risk of residual NMB or to resolve an ongoing case of residual NMB (patient safety rationale) (143 of 188; 76.1%) and reversal from deep block (132 of 188; 70.2%). Two-thirds (127 of 188; 67.6%) indicated that they had been administering sugammadex for more than 6 months. Approximately one-third (67 of 188; 35.6%) of respondents indicated that they had administered sugammadex to more than five patients.

Primary objective 1 of the survey was to measure anesthesiologist's knowledge of the appropriate use of sugammadex. Of the three questions being asked, two scored a > 95% correct response rate, and one question scored below the threshold of 75%. This question was a statement requiring participants to know that sugammadex is not indicated for use in children aged < 18 years (71.8%; 95% CI 65.0–77.9) (Table 1).

Primary objective 2 was to measure anesthesiologists' KAU of the safety and efficacy aspects of sugammadex. Of the eight questions being asked, seven scored a > 80% correct response rate, and one scored below the threshold of 75%. This question was a statement requiring participants

to know that monitoring is required for recurrence of NMB after reversal with sugammadex (73.3%; 95% CI 66.6–79.2) (Table 1).

The results for the 11 key questions that were analyzed by subgroups (stratified by sex, years of practice, reading/reviewing the sugammadex product monograph, participation in a Merck-sponsored educational program, or geographic region) had overlapping CIs, and no significant differences in subgroups were found (data not shown). However, this was a descriptive study without hypothesis testing, and the sample size was not powered to detect subgroup differences.

The five additional survey questions that were not considered part of the key objectives but were important concepts for anesthesiologists to know included questions involving knowledge around the use and storage of sugammadex. Of these five questions, four had an understanding rate of $\geq 88.1\%$. One question tested the concept that sugammadex is not recommended for use in patients with severe renal impairment (creatinine clearance [CrCl] < 30 mL/min), including those requiring dialysis; 60.4% of respondents answered this question correctly (see Table 1).

4 Discussion

Only two survey questions related to the primary objectives resulted in a correct response rate of < 75%. One question was associated with primary objective 1 and concerned the use of sugammadex being not indicated in children aged < 18 years. For this question, 71.8% (95% CI 65.0–77.9) of participants answered correctly, which suggests that the knowledge rate is likely to fall between 65.0 and 77.9%. The other question was associated with primary objective 2 and concerned the need for monitoring for recurrence of NMB after reversal with sugammadex. For this question, 73.3% (95% CI 66.6–79.2) of participants answered correctly, which suggests that the knowledge rate is likely to fall between 66.6 and 79.2%.

The third concept that did not meet the 75% threshold was not considered part of the key objectives but was nevertheless an important concept for anesthesiologists to know when treating patients with sugammadex. This concept was related to use in patients with severe renal impairment (CrCl < 30 mL/min), including those requiring dialysis (60.4% answered correctly).

This survey suggests that Canadian anesthesiologists in this sample generally had a good understanding of the safety and efficacy aspects of sugammadex. Certain knowledge points, as noted, highlighted ongoing areas for medical education among anesthesiologists. Following the survey completion, each participant who completed a survey was mailed a copy of the sugammadex product monograph for Canada

Table 1 Responses to all questions about the safe use of sugammadex

Primary objective	Question	Respondents (N=202)
1: understanding of appropriate use of BRIDION	BRIDION (sugammadex sodium) is indicated for reversal of moderate to deep neuromuscular blockade induced by rocuronium or vecuronium in adults undergoing surgery	
	True ^a	195 (96.5) [93.0–98.6]
	False	7 (3.5)
	BRIDION (sugammadex sodium) can be used to reverse blockade induced by nonsteroidal neuromuscular blocking agents such as succinylcholine or benzyisoquinolinium compounds (e.g., atracurium and cisatracurium)	
	True	5 (2.5)
	False ^a	197 (97.5) [94.3–99.2]
	BRIDION (sugammadex sodium) is indicated for use in children < 18 years of age	
	True	57 (28.2)
	False ^a	145 (71.8) [65.0–77.9]
2: understanding safety and efficacy of BRIDION	If rocuronium is re-administered after reversal with BRIDION (sugammadex sodium), the onset of neuromuscular blockade may be delayed and the duration of neuromuscular blockade may be shortened	
	True ^a	194 (96.0) [92.3–98.3]
	False	8 (4.0)
	Hypersensitivity reactions, ranging from isolated skin reactions to serious systemic reactions (i.e., anaphylaxis, or anaphylactic reactions), have occurred in individuals with or without prior exposure to BRIDION (sugammadex sodium)	
	True ^a	195 (96.5) [93.0–98.6]
	False	7 (3.5)
	Monitoring is not required for recurrence of neuromuscular blockade after reversal with BRIDION (sugammadex sodium)	
	True	54 (26.7)
	False ^a	148 (73.3) [66.6–79.2]
	Conditions associated with prolonged circulation time such as cardiovascular disease, old age, edematous state (e.g., severe hepatic impairment) may be associated with longer recovery times after administration of BRIDION (sugammadex sodium)	
	True ^a	170 (84.2) [78.4–88.9]
	False	32 (15.8)
	The depth of anesthesia does not need to be monitored and maintained whenever a neuromuscular relaxant is used, as well as when its effects are reversed with BRIDION (sugammadex sodium)	
	True	6 (3.0)
	False ^a	196 (97.0) [93.6–98.9]
	Since no cases of marked bradycardia have been reported following administration of BRIDION (sugammadex sodium), patients need not be monitored for hemodynamic changes during and after reversal of neuromuscular blockade	
	True	10 (5.0)
	False ^a	192 (95.0) [91.1–97.6]
	In one dedicated trial and in postmarketing data, in patients with a history of pulmonary complications, bronchospasm was reported as a possibly related adverse event	
	True ^a	167 (82.7) [76.7–87.6]
	False	35 (17.3)
	Use of BRIDION (sugammadex sodium) in adult patients with renal impairment: after retreatment with a steroidal NMBA, delayed onset of NMB may occur	
	True ^a	182 (90.1) [85.1–93.8]
	False	20 (9.9)

Table 1 (continued)

Primary objective	Question	Respondents (<i>N</i> =202)
Additional safety questions on BRIDION	BRIDION (sugammadex sodium) should be stored between 15 deg C to 30 deg C, protected from light	
	True ^a	178 (88.1) [82.8–92.2]
	False	24 (11.9)
	A dose of 16 mg/kg BRIDION (sugammadex sodium) is only recommended if there is an urgent or emergent need to reverse neuromuscular blockade following administration of a single dose of 1.2 mg/kg rocuronium for intubation	
	True ^a	187 (92.6) [88.0–95.8]
	False	15 (7.4)
	BRIDION (sugammadex sodium) should be administered by trained healthcare providers familiar with the use, actions, characteristics, and complications of neuromuscular blocking agents and neuromuscular block reversal agents	
	True ^a	201 (99.5) [97.3–1.00]
	False	1 (0.5)
	Ventilator support is mandatory for patients until adequate spontaneous respiration is restored following reversal of neuromuscular blockade with BRIDION (sugammadex sodium)	
	True ^a	196 (97.0) [93.6–98.9]
	False	6 (3.0)
	BRIDION (sugammadex sodium) is recommended for use in patients with severe (<i>CrCl</i> <30 mL/min) renal impairment, including those requiring dialysis	
	True	80 (39.6)
	False ^a	122 (60.4) [53.3–67.2]

Data are presented as *n* (%) [95% confidence interval]

CrCl creatinine clearance

^aCorrect response

and a document listing the desired responses to the safety and efficacy aspects related to sugammadex administration in the anesthesiologist's clinical practice. This educational outreach was intended to bridge the knowledge gap for the participating anesthesiologists regarding the use, safety, and efficacy of sugammadex.

The survey had a few strengths as a number of controls were put in place to ensure the survey was conducted in a professional manner and to minimize bias. First, the survey was programmed to ensure that questions were asked in the appropriate sequence. Questions were presented in a standard order for both modes of survey administration. All questions were required to be answered in the order displayed for the respondent to complete a survey. Second, respondents could not go back to a question once the question had been answered and could not skip ahead. Third, respondents were provided with a unique code during the recruitment process to gain access to the system via the internet or to provide when calling the survey coordinating center. The code was inactivated after use to minimize exposure bias and fraud. Fourth, a standardized script was used for telephone interviews, and all telephone interviewers were trained in

interview techniques. Fifth, lists of response options for both modes of survey administration were randomized to minimize the potential for positional bias. Finally, programming for both modes of survey administration was reviewed by quality control and simulated users (user acceptance testing) before the survey was implemented.

However, the survey also had limitations. Although the survey met its target sample size, the overall response rate was low. Per the more than 16,000 knowledge surveys performed by UBC (the survey vendor), this response rate is in the expected response range for survey of healthcare professionals. The survey participants were self-selected because they voluntarily responded to the invitation to participate in the survey, so the potential existed that those who chose to respond to the survey may differ in their understanding of the important safety information from those who elected not to participate. This is a common limitation of all studies that rely on voluntary participation.

Second, while the survey can be used to assess anesthesiologists' understanding of important safety information, it cannot clearly determine the channel via which the anesthesiologists gained the information. Among those who

volunteered to respond to the survey, recall of information was critical. Inherent in survey research is the reliance on the respondent's recall of whether or not a Merck-sponsored educational program related to sugammadex and/or the sugammadex product monograph for Canada was received. However, it was possible that respondents simply may not have recalled participating in a Merck-sponsored educational program related to sugammadex or whether they had reviewed the sugammadex product monograph for Canada. It was also possible that the participants had acceptable understanding of the important safety and efficacy aspects despite not recalling attendance at a Merck-sponsored educational program related to sugammadex and/or reviewing the sugammadex product monograph for Canada. Nevertheless, the study results showed no significant difference in knowledge rate across subgroup analyses when stratified by reading the sugammadex product monograph for Canada or by participating in the Merck-sponsored educational programs.

The third limitation is that the proposed survey questionnaire was not evaluated through pilot testing among the appropriate target respondents. While pilot testing of surveys is important, the language for most of the questions was directly extracted from the sugammadex product monograph for Canada. Therefore, it was deemed unnecessary to further evaluate the wording for clarity and comprehension, particularly since the survey was targeting anesthesiologists who had either self-identified as having completed a Merck-sponsored educational program or administering sugammadex in the 12 months before survey launch.

5 Conclusion

In general, the survey results suggested that anesthesiologists, whether through reading the Canadian sugammadex product monograph, attending a Merck-sponsored educational program, or experience gained by administering sugammadex, understood the use, safety, and efficacy of sugammadex for the reversal of moderate to deep NMB induced by rocuronium or vecuronium in adults undergoing surgery.

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Compliance with Ethical Standards

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Conflict of interest AS and MJ are employees of United BioSource LLC, which received funding from Merck to collect data and perform the analyses. PB, WZ, GD, and CK are employees of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA, all of whom may own stock and/or hold stock options in the company.

Data availability statement This study is registered on ENCEPP (<http://www.encepp.eu/>, registration number: EUPAS24076), where the study protocol and the full study report can be accessed.

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