Perioperative outcome and smart monitors

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Chapter 5

Chapter 5. Sugammadex related cardiac adverse events, a narrative review of reported cases

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5.1. Abstract

Sugammadex, a modified y-cyclodextrin, is capable to rapidly terminate neuromuscular block at the end of anaesthesia. Since its introduction in clinical practice, it has gained widespread adoption for this purpose. Although sugammadex is generally considered to be safe, it may be linked to a number of potentially fatal cardiac dysrhythmias, according to growing clinical data. The pathophysiology of these sugammadex-associated cardiac events are however unknown. To increase our knowledge and understanding on this topic, we searched recent literature for cases of (potential) sugammadex-associated cardiac adverse events and review possible pathophysiological mechanisms. Bradycardia was the prevailing arrythmia in this search, although tachyarrhythmias, ventricular fibrillation and ST-segmental changes were also reported. Most arrythmias were related to anaphylaxis. Arrythmias were also more likely to occur in patients with cardiac comorbidities. It is crucial that care givers are aware of these potentially serious problems even if adverse cardiac events are uncommon and do not call for a change in current practice.

5.2. Introduction

Neuromuscular blocking agents (NMBAs) are routinely administered during anaesthesia to facilitate intubation and to enhance surgical conditions[1,2]. The use of NMBAs comes with the risk of postoperative respiratory complications if muscle relaxation persists after extubation[3,4]. Reversal agents such as sugammadex or acetylcholinesterase inhibitors (e.g. neostigmine) may be administered to antagonize any residual NMB prior to extubation at the end of surgery. Sugammadex differs from traditional competitive reversal agents in that it permanently encapsulates amino-steroidal NMBAs, such as rocuronium, vecuronium, pancuronium or pipecuronium in plasma. Encapsulation effectively lowers the free plasma NMBA concentration, creating a diffusion gradient with the peripheral compartment causing a rapid reduction of the NMBA concentration at the neuromuscular junction as well[5-11]. In comparison to acetylcholinesterase inhibitors, sugammadex outperforms significantly with respect to reversal

time and cardiovascular side-effects[7,12,13]. The majority of sugammadex-related side-effects in phase 1 and 2 trials entailed drug hypersensitivity reactions, dysgeusia (distortion of sense or taste) and nausea[7,9,12,14-16]. Therefore, no major sugammadex-related cardiovascular effects were predicted upon its introduction to clinical practice. Nevertheless, numerous potentially fatal cardiac adverse events that may have been connected to the administration of sugammadex have been documented ever since[17-21]. Although some cardiac arrhythmias were related to drug hypersensitivity[18,19], the majority of cardiac adverse events have uncertain pathophysiological causes[17,20,21]. For the purpose of this review, we searched the recent literature to determine the types of sugammadex-associated cardiac events and potential mechanisms underlying these events.

5.3. Methods

In May 2021 we conducted a systematic computerized search, without date range limits, of PubMed, Embase, Web of Science, Cochrane Library, Emcare and Academic Search Premier databases for manuscripts that reported sugammadex-related cardiac adverse events. The search terms included 'sugammadex', 'bridion', 'bradycardia', 'asystole' and 'arrhythmia' (full search is enclosed in Appendix 1). The search strategy was registered in Prospero under identifier CRD42020147221. In this search, bradycardia was defined as a reduction in heart rate below 60 beats/minute, occurring within minutes after sugammadex administration. Since the majority of included manuscripts consisted of case descriptions of arrythmias in phase II-IV trials and case reports, we opted for a narrative review of the reported cases. In this review, we focus on the prevalence, type and mechanisms of sugammadex-related cardiac arrythmias during general anaesthesia.

Cardiac Adverse Events in Case Reports

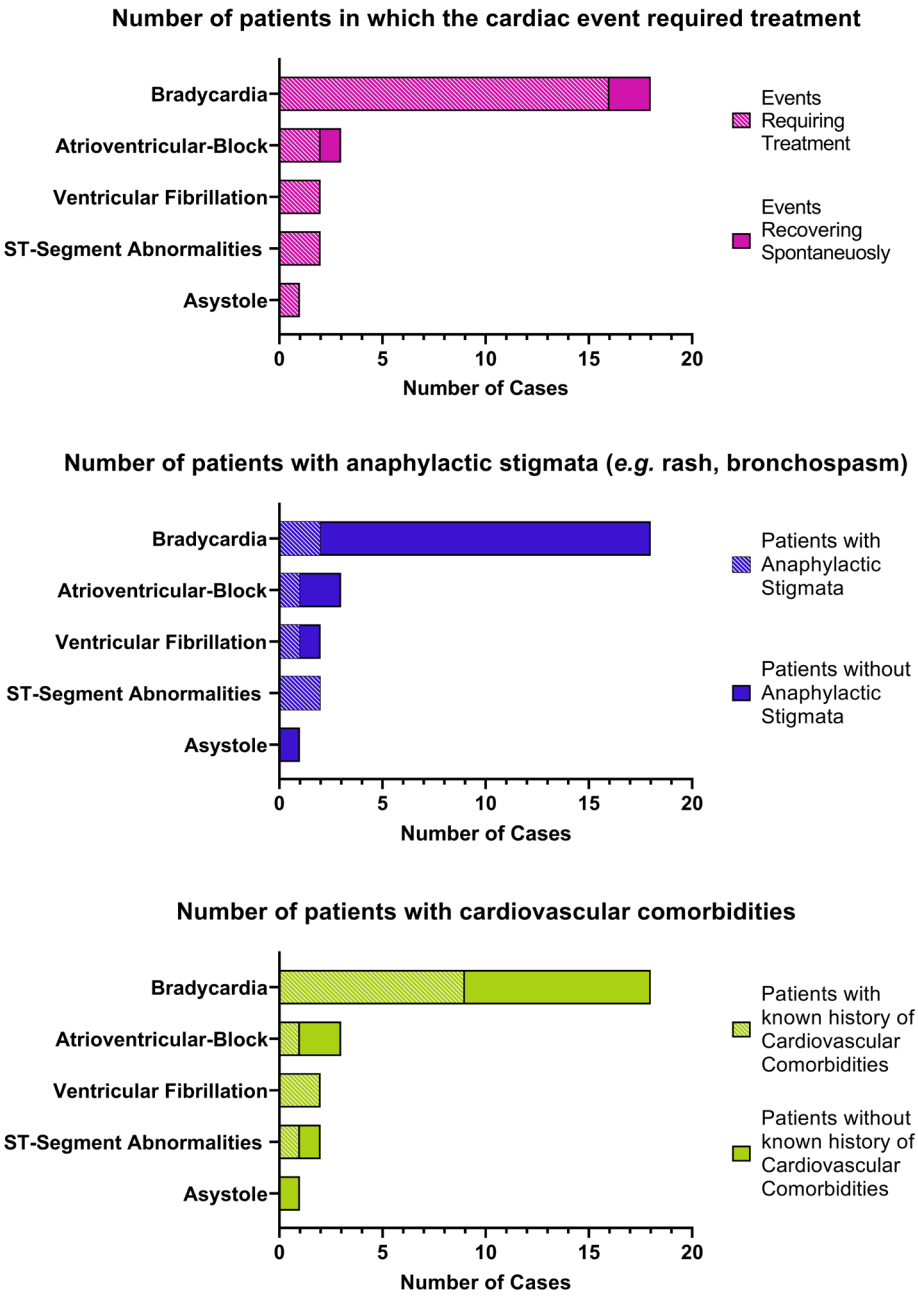

Figure 7. Cardiac adverse events in case reports.

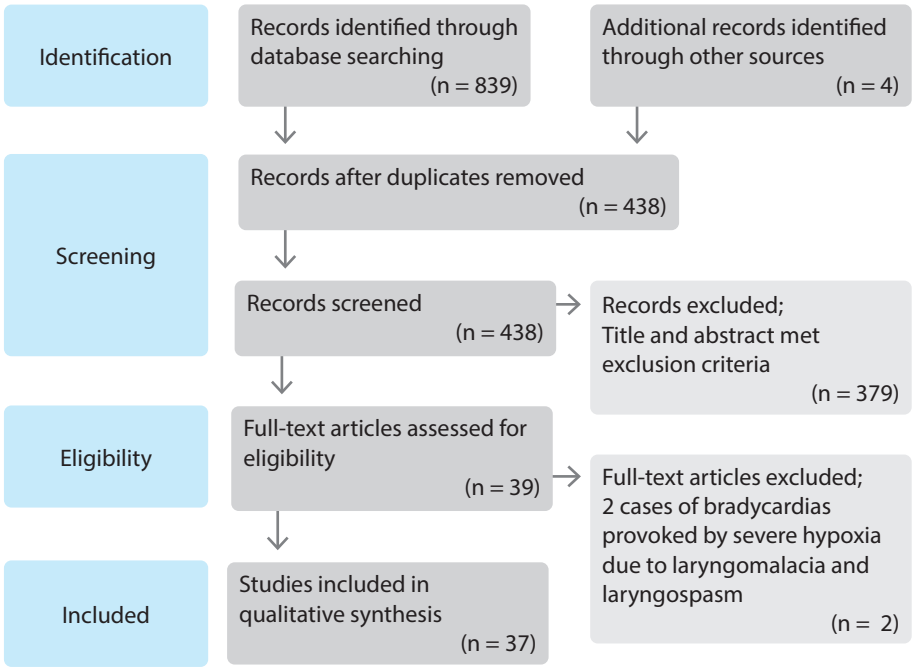

Figure 8. PRISMA Study flow diagram of selected records.

5.4. Results

The search and selection process resulted in 33 papers (see figure 8), that comprised nine prospective trials[12,15,22-28], one retrospective study[29] and twenty three case reports[20,21,30-50]. A supplementary search of the selected manuscripts' reference lists revealed two additional prospective trials[51,52] and two additional case reports[17,53]. From all papers, we identified 155 unique patients that had a sugammadex-associated cardiac event. We present the data from the prospective and retrospective studies in Table 4 [12,15,22-29,51,52] and provide the data from the case reports in Table 5 and Figure 7 [17,20,21,30-50,53]. An overview of the general characteristics of all reported cases is provided in Table 6.

5.4.1. Characteristics of sugammadex related cardiac adverse events

All sugammadex-related adverse events occurred after reversal of a neuromuscular block induced by either rocuronium or vecuronium. Table 6 displays that the median time between sugammadex administration and the cardiac event was 2 minutes with a range of 0 to 30 min. The most often reported cardiac adverse event was bradycardia[12,15,17,21-35,37-41,46,47,49-53]. Occasionally, these bradycardias were followed by a cardiac arrest[31,33,40,41,46,47] or ST-segment abnormality[21,49,50]. Other types of cardiac events included: atrioventricular-blockade[20,44,45], ventricular fibrillation[36,48] or a primary ST-segment abnormality[42,43].

Of all reported cases, 26 patients required medical treatment, with our without cardiopulmonary resuscitation[12,17,20,21,24,26,30-33,35-38,40-43,45-50,53], while 17 patients required admission to an intensive care unit for prolonged hemodynamic support or postoperative observation[20,21,30-33,35-38,41,42,46-50]. One patient died due to progression of bradycardia to pulseless electric activity[40].

5.5. Discussion

We report on a series of cases (n = 155) of sugammadex-associated cardiac adverse events that occurred early on (medium time to event 2 min) after administration of the reversal agent, although intervals up to 25 minutes have been reported as well. A considerable number of patients required cardiopulmonary resuscitation or admission to an intensive care unit subsequent to the cardiac adverse event. Our findings indicate that the consequences of a sugammadex-associated event may be severe; the pathophysiological mechanisms that may explain these events are discussed below.

Table 4. Prospectieve studies.

Author	Study Characteristics	Patients Treated with Sugammadex (N)	Cardiac Event	Event Outcome	Sugammadex-Cardiac Event Time interval
	Prospective cohort studies				
Alsuhebani et al. 2020	Endpoint: bradycardia incidence	221	Eighteen cases of bradycardia	Spontaneous recovery without sequalae	Median 2 minutes [range 1-25]
Arends et al. 2020	Paediatric population Endpoint: bradycardia incidence	99	Fourteen cases of bradycardia	Spontaneous recovery without sequalae	Unknown
Sims et al. 2020	Paediatric population Endpoint: bradycardia incidence	200	Thirteen cases of bradycardia	One patient was treated with ephedrine, outcome not reported	Median 5 minutes [range 2-25]
	Randomized controlled sugammadex dose-finding trials				
Vanacker et al. 2007	Phase II safety trial	42	One case of bradycardia	Treatment or outcome not reported	Not reported
Groudine et al. 2007	Phase II dose-finding trial	50	One case of bradycardia	Successfully treated with glycopyrrolate 0.4 mg	2 minutes
Pühringer et al. 2008	Phase II dose-finding trial	157	Three cases of bradycardia	Treatment or outcome of bradycardias not reported	Unknown
Schaller et al. 2010	Phase III dose-finding trial	43	One case of bradycardia	Treated with glycopyrrolate 0.2 mg, outcome not reported	Unknown
Woo et al. 2013	Phase IV safety trial	60	One case of bradycardia	Treatment or outcome not reported	Unknown
Wu et al. 2014	Phase IV safety trial	149	One case of bradycardia	Treatment or outcome not reported	Unknown
Koyuncu et al. 2015	Phase IV safety trial	50	One case of bradycardia	Treatment or outcome not reported	Unknown
Yazar et al. 2016	Phase IV safety trial	60	Four cases of bradycardia	Treatment or outcome not reported	Unknown
	Retrospective cohort study				
Gayer et al. 2019	Paediatric population Endpoint: bradycardia incidence	968	Seventy-one cases of bradycardia after sugammadex administration	Treatment or outcome not reported	Unknown

Author	Chronological Cardiac Event Description	Time to event[a]	Vasopressors Administered[b]	CPR	ICU Admission	Patient outcome[c]	Anaphylactic Stigmata[d]	Comorbidity
Samara et al. 2020	Asystole	-	Yes	Yes	Yes	Full Recovery	-	Tobacco abuse
Osaka et al. 2012	2nd degree AV-block; converted to 1st degree AV-block	-	-	-	-	Spontaneous conversion to sinus rhythm; further outcome unknown	-	-
Saito et al. 2015	3rd degree AV-block	4 minutes	Yes	-	-	Outcome unknown	-	-
Iwade et al. 2014	Complete AV-block	2 minutes	Yes	Yes	Yes	Full recovery	Erythema	CABG, hypertension, atrial fibrillation
Bilgi et al. 2014	Bradycardia	2 minutes	Yes	-	-	Full recovery	-	-
Ho et al. 2016	Bradycardia	-	Yes	-	Yes	Full recovery	Intradermal rocuronium-sugammadex test positive	Asthma
Ko et al. 2016	Bradycardia & PVCs	2 minutes	Yes	Yes	Yes	Full recovery	-	Variant angina
King et al. 2017	Bradycardia	30 seconds	Yes	Yes	Yes	Full recovery	-	Heart transplantation, epilepsy
Shin et al. 2017	Bradycardia	3 minutes	Yes	-	-	Full recovery	-	Premature atrial contractions
Bhavani et al. 2018	Bradycardia; Pulseless Electric Activity	2 minutes	Yes	Yes	Yes	Discharged to ward, passed away post-op day 15 due to declining general condition	-	Disseminated small cell lung carcinoma
Bhavani et al. 2018	Bradycardia; Sinus-arrest	1 minute	Yes	Yes	-	Full recovery	-	Cerebrovascular accident, hypertension, asthma, dyslipidaemia, hypothyroidism, chronic kidney disease, tobacco abuse
Bedirli et al. 2018	Bradycardia, PVCs & tachycardia	1 minute	Yes	-	Yes	Full recovery	Rash & bronchospasm	Weaver syndrome, atrial septal defect
Makris et al. 2018	Bradycardia	40 seconds	-	-	-	Full recovery	-	Angelman syndrome
Sanoja et al. 2019	Bradycardia; Pulseless Electric Activity	1 minute	Yes	Yes	Yes	Full recovery	-	Controlled hypertension
Gajewski et al. 2019	Bradycardia	30 seconds	-	-	-	Spontaneous conversion to sinus rhythm; full recovery	-	Type 2 diabetes mellitus, obesity, tracheomalacia & stenoses
Choi et al. 2019	Bradycardia	2 minutes	Yes	-	Yes	Full recovery	-	Hypertension, diabetes mellitus, kidney failure, 1st degree AV-block
Kikura et al. 2019	Bradycardia, ST-elevation & Ventricular Fibrillation	10 minutes	Yes	Yes	Yes	Full recovery after coronary balloon angioplasty	Pruritis and urticaria	Myocardial infarction, hypertension, diabetes mellitus

Author	Chronological Cardiac Event Description	Time to event[a]	Vasopressors Administered[b]	CPR	ICU Admission	Patient outcome[c]	Anaphylactic Stigmata[d]	Comorbidity
Nguyen et al. 2020	Bradycardia; sinus-arrest	30 minutes	-	Yes	Yes	Full recovery	-	-
Yoshida et al. 2020	Bradycardia & ST-depression	3 minutes	Yes	-	Yes	Full recovery	-	Obesity
Yilmaz et al. 2020	Bradycardia & ST- depression & PVCs	1 minute	Yes	-	Yes	Full Recovery	-	Tobacco abuse
Mirza et al. 2020	Bradycardia; Pulseless Electric Activity	-	Yes	Yes	-	Deceased	-	Chronic obstructive pulmonary disease, hypertension, dyslipidaemia and tobacco abuse
Fierro et al. 2021	Bradycardia; Sinus-arrest	1 minute	Yes	Yes	Yes	Full Recovery	-	Hypothyroidism, hyperuricemia, diabetes and chronic obstructive pulmonary disease
Obara et al. 2018	ST-depression & polymorphic PVCs; cardiac-arrest	6 minutes	Yes	Yes	Yes	Full recovery	Intradermal sugammadex test positive	Paroxysmal atrial fibrillation
Okuno et al.[e] 2018	ST-elevation & Tachycardia; potential coronary vasospasm	2 minutes	Yes	-	-	Full recovery	Intradermal rocuronium-sugammadex test positive	-
Kim et al. 2018	Ventricular Fibrillation; Coronary vasospasm	2 minutes	Yes	Yes	Yes; VA-ECMO	Full recovery	-	Valvular heart disease, heart failure, chronic kidney disease
Yanai et al.[e] 2020	Ventricular Fibrillation & Coronary vasospasm	13 minutes	Yes	Yes	Yes	Full recovery	Intradermal sugammadex test positive	Paroxysmal atrial fibrillation, cerebrovascular accident

Table 5. Case Reports. a: Time interval between sugammadex administration and the reported cardiac adverse event; b: Intervention of events with vasoactive agent consisted of either inotropics or vasopressors; c: Full recovery = patient is discharged from the hospital without sequela; d: Anaphylaxis is (suspected) based on clinical symptomatology or diagnosed with positive skin tests; e: Okuno et al. and Yanai et al. report two different sugammadex associated cardiac adverse events in two successive procedures within the same patient. Abbreviations: AV-block = atrioventricular block. CABG = coronary artery bypass graft. CPR = cardiopulmonary resuscitation. ECG = electrocardiogram. ICU = intensive care unit. PVCs = premature ventricular contractions. TOF = train-of-four. - = information not reported or intervention not performed.

Patient & Event Characteristics (n = number of cases)		Prospective Trials (n = 58)	Retrospective Studies (n = 71)	Case Reports (n = 26)	Cumulative Cases (n= 155)
Event type [requiring intervention]	Bradycardia (n)	58 [3]	71 [-]	18 [16]	147 [19]
	Atrioventricular-block (n)	0	0	3 [2]	3 [2]
	Ventricular fibrillation (n)	0	0	2 [2]	2 [2]
	Anaphylactic arrythmias accompanied by ST-segment abnormalities (n)	0	0	2 [2]	2 [2]
	Asystole (n)	0	0	1 [1]	1 [1]
Cumulative Sugammadex Dosage (mg kg -1)	Median [range]	2.0 [2.0-8.0]	-	2.6 [2.0-8.8]	2.4 [2.0-8.8]
	Missing (n)	49	71	2	122
Time to Event in Minutes	Median [range]	2 [2-2]	-	2 [0-30]	2 [0-30]
	Missing (n)	57	71	4	132

Table 6. General Characteristics.

5.5.1. Anaphylaxis and cardiac arrythmias

In seven case reports, sugammadex-associated cardiac events were accompanied by symptoms of anaphylaxis, such as the development of a rash, pruritus or bronchospasm[20,21,30,35,42,43,48]. Intradermal testing confirmed hypersensitivity in most[35,42,43,48] but not all cases[20,21,30]. This suggests that sugammadex may activate both IgE-mediated (i.e. genuine anaphylaxis) and non-IgE-mediated (i.e. anaphylactoid reaction) pathways. These reactions may evoke a variety of cardiac abnormalities, including bradycardia[35], polymorphic premature ventricular contractions[42] or coronary vasospasms[43,48]. Although, tachycardia and hypotension are the classical cardiovascular symptoms of anaphylaxis[54], cardiac ischemia and atypical ventricular arrhythmias have been described in relation to anaphylactic reactions as well[55,56]. The release of IgE-mediated factors during these reactions, such as histamine or platelet activating factor (PAF), may induce hypotension, atrioventricular block, bradycardia and ST-segment alterations[57-61], or coronary vasospasms in patients with angina pectoris[62].

An acute coronary anaphylactic syndrome, the Kounis syndrome, may also cause a range of dysrhythmias. In this specific syndrome, an inflammatory response is triggered by either an allergic, hypersensitivity, anaphylactic or anaphylactoid reaction and causes mast cells to interact with macrophages and T-lymphocytes[63]. This results in release of vasoactive inflammatory mediators, that induce cardiac arrythmias and coronary vasospasm, resulting in brady- and tachyarrhythmias, ventricular fibrillation and/or cardiac arrest[63-66]. As described

in a case report on a patient that suffered from coronary vasospasms after sugammadex administration, the anaphylactic component in this ischemic coronary event is often unrecognized[43]. This particular patient developed arrythmias and coronary vasospasms on two separate occasions following two sugammadex infusions. Initially, the cause and relationship with sugammadex remained unnoticed. After the second exposure to sugammadex the patient developed generalized erythema, and the subsequent coronary vasospasms were related to sugammadex-mediated hypersensitivity[43]. When the Kounis syndrome is suspected, treatment must focus on coronary reperfusion and treatment of the hypersensitivity reaction with corticosteroids and antihistamines[63].

5.5.2. Sugammadex related cardiac adverse events in patients with cardiovascular comorbidities

Two prospective studies described an increased incidence of bradycardia following sugammadex infusion in paediatric patients with cardiomyopathies or congenital heart disease[22,23]. In other reports, half of the patients with severe bradycardia, atrioventricular-block, ventricular fibrillation or ST-segment abnormalities had comorbid cardiovascular conditions: valvular- and coronary heart disease, atrial septal defects, pre-existing cardiac arrhythmias, angina and hypertension[20,21,30-32,36-38,40,42,47,48,53]. These observations suggest that patients with concomitant cardiovascular comorbidities may be more susceptible to sugammadex-related cardiac arrythmias. This theory is supported by several studies on the occurrence of anaphylactic response in patients with cardiovascular comorbidities[67-69]. These studies show that patients with cardiomyopathy and coronary disease have elevated coronary mast cells concentrations and serum histamine levels. Higher mast cell levels may yield an exaggerated IgE-mediated response after an anaphylactic trigger, which can result in cardiac arrhythmias and coronary vasospasms subsequent to mast cell degranulation[62,69].

Finally, we included one case report in which a patient with a transplanted heart developed a bradycardia shortly after sugammadex administration[37]. An important benefit of sugammadex is that, in contrast to cholinesterase inhibitors, there are no associated cholinergic side effects as sugammadex works directly on the NMBA rather than interfering with cholinergic (neuro)transmission. This

is especially advantageous in the denervated heart, which is mostly regulated by plasma sympathetic hormones[70]. In addition, previous in vitro isothermal titration calorimetry suggests that that there is no relevant interaction between sugammadex and sympathomimetic hormones[71]. As such, sugammadex has been used safely in cardiac transplanted patients[72], and the case report that was included in our selection does not correspond to that case. We contend however, that the reported bradycardia may have been tainted by the concomitant administration of dexmedetomidine in this particular case.

5.5.3. Allosteric effects at cardiac receptors by NMBAs

Certain amino-steroidal NMBAs, such as pancuronium and gallamine, affect heart rate[73-75], through effects at parasympathetic cardiac muscarinic M2-receptors[76,77]. In-vitro experiments have shown that the aminosteroidal NMBAs gallamine, vecuronium and pancuronium possess negative allosteric properties at the M2-receptor[78], indicating that they reduce the affinity of M2-receptor agonists acetylcholine by modulating the ligand binding site. The allosteric modulation of these agents at the sinoatrial node is thought to increase heart rate by a reduction of the parasympathetic tone. Consequently, a reduction of the allosteric effect at the M2-receptor, as would be the case when sugammadex quickly terminates the effects of these NMBAs, would, in theory, lead to a decrease in heart rate as the parasympathetic effect on heart rate recovers. However, we did not find any case reports describing bradycardia following reversal of pancuronium induced neuromuscular block. In addition, we contend that this interaction is irrelevant in case rocuronium or vecuronium is used.

5.5.4. Bradycardia during emergence of anaesthesia

Recovery from anaesthesia is accompanied by significant changes in the parasympathetic-sympathetic balance. A reduction in sympathetic activity from the loss of surgical stimulation[79], or an increase in parasympathetic tone from the termination of mechanical ventilation[80], may affect heart rate. An additional effect may relate to the return of muscle spindle afferentation. A recent observational study on the effects of sugammadex on the R-R interval observed

that in all 55 patients, heart rate dropped after sugammadex was administered at the end of anesthesia[81]. The authors related the heart rate reduction to an autonomic response, which is triggered by a sugammadex-mediated activation of muscle stretch receptors. The afferent input from these muscle spindles will affect autonomous cardiac reflexes, which, in this case, results in reduced heart rate. Additionally, the reversal of muscle spindle deafferentation may improve the recovery of consciousness (as is visible in the electroencephalogram) [82] and improve postoperative cognitive recovery and is thought to improve postoperative cognitive recovery[83]. Finally, also muscle contractions after return of consciousness may affect heart rate and blood pressure due to an increase in venous return and subsequent rebalancing of the sympathetic-parasympathetic tone.

5.5.5. Clinical consequences of sugammadex related cardiac adverse events

Summarizing, after reviewing the literature, we found that the most prevalent sugammadex-associated cardiac adverse event is bradycardia. Less prevalent are atrioventricular-blockade, ventricular-fibrillation or ST-segment abnormalities. Several cardiac arrythmias were related to sugammadex hypersensitivity. These findings call on anaesthesia care providers to consider anaphylaxis as cause of cardiac arrythmias and ischemic events after sugammadex infusion, as an anaphylaxis requires specialized treatment.

We also noted that sugammadex-associated bradycardia was prevalent among patients with cardiovascular comorbidities. In agreement with these findings, a large retrospective pharmacovigilance database analyses of sugammadex-related adverse events also noted an increase in fatal adverse drug reactions, including arrythmias, in patients with cardiac disorders[84]. This may suggest that, compared to healthy individuals, patients with cardiovascular comorbidities are more prone to drug hypersensitivity.

Fortunately, the incidence of fatal adverse events following sugammadex administration appears to be quite low compared to the millions of patients that received sugammadex worldwide[85]. Furthermore, a recent cohort study showed that neostigmine and sugammadex are comparably safe regarding postoperative side effects such as cardiac arrythmias[86]. Based on our findings and currently

available literature we do not recommend to restrict the use of sugammadex for reasons of cardiac safety and we contend that there is no necessity to alter current NMB reversal practice.

5.6. Limits

We are aware that due to the retrospective nature of our narrative review no definitive conclusions can be drawn regarding the mechanism underlying treatment emergent adverse events. All cases discussed in this review originate from case-descriptions in randomized controlled trials and case reports and are thereby prone to reporting bias and missing data. Therefore, other reasons for the cardiac adverse events other than the topics discussed in this review could have triggered the cardiac effects.

5.7. Conclusion

In conclusion, sugammadex-associated cardiac adverse events are a rare but potentially life-threatening medical condition. The severity of the reported cases underlines that the anaesthesia care giver need to be vigilant for arrythmias and ischemic cardiac events following sugammadex infusion, particularly in patients with cardiac comorbidities. In addition, we advocate that anaphylaxis should be considered early on in sugammadex-associated cardiac adverse events, especially since treatment of anaphylactic ischemic cardiac events may require immediate coronary reperfusion.

5.8. References

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5.9. Appendix 1: full search criteria per database

PubMed

((“Sugammadex”[mesh] OR “sugammadex”[tw] OR sugammadex*[tw] OR “Org 25969”[tw] OR “Bridion”[tw]) AND (“Bradycardia”[Mesh] OR “bradycardia”[tw] OR Bradycardia*[tw] OR “Bradyarrhythmia”[tw] OR Bradyarrhythm*[tw] OR “Coronary Vasospasm”[Mesh] OR “Coronary Vasospasm”[tw] OR “Coronary Vasospasms”[tw] OR “Coronary Artery Vasospasm”[tw] OR “Coronary Artery Vasospasms”[tw] OR “Heart Arrest”[Mesh] OR “Heart Arrest”[tw] OR “Cardiac Arrest”[tw] OR “Asystole”[tw] OR Asystol*[tw] OR “Cardiopulmonary Arrest”[tw] OR “Arrhythmias, Cardiac”[Mesh] OR “Arrhythmias”[tw] OR Arrhythm*[tw] OR Atrioventricular Block*[tw] OR Heart Block*[tw]) NOT (“Animals”[mesh] NOT “Humans”[mesh]))

Embase

((“Sugammadex”/ OR “sugammadex”.mp OR sugammadex*.mp OR “Org 25969”.mp OR “Bridion”.mp) AND (exp “Bradycardia”/ OR “bradycardia”.mp OR Bradycardia*.mp OR “Bradyarrhythmia”.mp OR Bradyarrhythm*.mp OR exp “Heart Arrhythmia”/ OR “Arrhythmias”.mp OR Arrhythm*.mp OR “Coronary artery spasm”/ OR “Coronary Vasospasm”.mp OR “Coronary Vasospasms”.mp OR “Coronary Artery Vasospasm”.mp OR “Coronary Artery Vasospasms”.mp OR exp “Heart Arrest”/ OR “Heart Arrest”.mp OR “Cardiac Arrest”.mp OR “Asystole”.mp OR Asystol*.mp OR “Cardiopulmonary Arrest”.mp OR Atrioventricular Block*.mp OR Heart Block*.mp) NOT (exp “Animals”/ NOT exp “Humans”/))

Web of Science

(ts=(“Sugammadex” OR “sugammadex” OR sugammadex* OR “Org 25969” OR “Bridion”) AND ts=(“Bradycardia” OR “bradycardia” OR Bradycardia* OR “Bradyarrhythmia” OR Bradyarrhythm* OR “Heart Arrhythmia” OR “Arrhythmias” OR Arrhythm* OR “Coronary artery spasm” OR “Coronary Vasospasm” OR “Coronary Vasospasms” OR “Coronary Artery Vasospasm” OR “Coronary Artery Vasospasms” OR “Heart Arrest” OR “Heart Arrest” OR “Cardiac Arrest” OR “Asystole” OR Asystol* OR “Cardiopulmonary Arrest” OR “Atrioventricular Block*” OR “Heart Block*”) NOT ti=(“veterinary” OR “rabbit” OR “rabbits” OR “animal” OR “animals” OR “mouse” OR “mice” OR “rodent” OR “rodents” OR “rat” OR “rats” OR “pig” OR “pigs” OR “porcine” OR “horse” OR “horses” OR “equine” OR “cow” OR “cows” OR “bovine” OR “goat” OR “goats” OR “sheep” OR “ovine” OR “canine” OR “dog” OR “dogs” OR “feline” OR “cat” OR “cats”))

Cochrane

((“Sugammadex” OR “sugammadex” OR sugammadex* OR “Org 25969” OR “Bridion”) AND (“Bradycardia” OR “bradycardia” OR Bradycardia* OR “Bradyarrhythmia” OR Bradyarrhythm* OR “Heart Arrhythmia” OR “Arrhythmias” OR Arrhythm* OR “Coronary artery spasm” OR “Coronary Vasospasm” OR “Coronary Vasospasms” OR “Coronary Artery Vasospasm” OR “Coronary Artery Vasospasms” OR “Heart Arrest” OR “Heart Arrest” OR “Cardiac Arrest” OR “Asystole” OR Asystol* OR “Cardiopulmonary Arrest” OR “Atrioventricular Block*” OR “Heart Block*”)):ti,ab,kw

Emcare

((“Sugammadex”/ OR “sugammadex”.mp OR sugammadex*.mp OR “Org 25969”.mp OR “Bridion”.mp) AND (exp “Bradycardia”/ OR “bradycardia”.mp OR Bradycardia*.mp OR “Bradyarrhythmia”.mp OR Bradyarrhythm*.mp OR exp “Heart Arrhythmia”/ OR “Arrhythmias”.mp OR Arrhythm*.mp OR “Coronary artery spasm”/ OR “Coronary Vasospasm”.mp OR “Coronary Vasospasms”.mp OR “Coronary Artery Vasospasm”.mp OR “Coronary Artery Vasospasms”.mp OR exp “Heart Arrest”/ OR “Heart Arrest”.mp OR “Cardiac Arrest”.mp OR “Asystole”.mp OR Asystol*.mp OR “Cardiopulmonary Arrest”.mp OR Atrioventricular Block*.mp OR Heart Block*.mp) NOT (exp “Animals”/ NOT exp “Humans”/))

Academic Search Premier

(TI("Sugammadex" OR "sugammadex" OR sugammadex* OR "Org 25969" OR "Bridion") AND TI("Bradycardia" OR "bradycardia" OR Bradycardia* OR "Bradyarrhythmia" OR Bradyarrhythm* OR "Heart Arrhythmia" OR "Arrhythmias" OR Arrhythm* OR "Coronary artery spasm" OR "Coronary Vasospasm" OR "Coronary Vasospasms" OR "Coronary Artery Vasospasm" OR "Coronary Artery Vasospasms" OR "Heart Arrest" OR "Heart Arrest" OR "Cardiac Arrest" OR "Asystole" OR Asystol* OR "Cardiopulmonary Arrest" OR "Atrioventricular Block*" OR "Heart Block*") NOT TI("veterinary" OR "rabbit" OR "rabbits" OR "animal" OR "animals" OR "mouse" OR "mice" OR "rodent" OR "rodents" OR "rat" OR "rats" OR "pig" OR "pigs" OR "porcine" OR "horse" OR "horses" OR "equine" OR "cow" OR "cows" OR "bovine" OR "goat" OR "goats" OR "sheep" OR "ovine" OR "canine" OR "dog" OR "dogs" OR "feline" OR "cat" OR "cats")) OR (SU("Sugammadex" OR "sugammadex" OR sugammadex* OR "Org 25969" OR "Bridion") AND SU("Bradycardia" OR "bradycardia" OR Bradycardia* OR "Bradyarrhythmia" OR Bradyarrhythm* OR "Heart Arrhythmia" OR "Arrhythmias" OR Arrhythm* OR "Coronary artery spasm" OR "Coronary Vasospasm" OR "Coronary Vasospasms" OR "Coronary Artery Vasospasm" OR "Coronary Artery Vasospasms" OR "Heart Arrest" OR "Heart Arrest" OR "Cardiac Arrest" OR "Asystole" OR Asystol* OR "Cardiopulmonary Arrest" OR "Atrioventricular Block*" OR "Heart Block*") NOT TI("veterinary" OR "rabbit" OR "rabbits" OR "animal" OR "animals" OR "mouse" OR "mice" OR "rodent" OR "rodents" OR "rat" OR "rats" OR "pig" OR "pigs" OR "porcine" OR "horse" OR "horses" OR "equine" OR "cow" OR "cows" OR "bovine" OR "goat" OR "goats" OR "sheep" OR "ovine" OR "canine" OR "dog" OR "dogs" OR "feline" OR "cat" OR "cats")) OR (KW("Sugammadex" OR "sugammadex" OR sugammadex* OR "Org 25969" OR "Bridion") AND KW("Bradycardia" OR "bradycardia" OR Bradycardia* OR "Bradyarrhythmia" OR Bradyarrhythm* OR "Heart Arrhythmia" OR "Arrhythmias" OR Arrhythm* OR "Coronary artery spasm" OR "Coronary Vasospasm" OR "Coronary Vasospasms" OR "Coronary Artery Vasospasm" OR "Coronary Artery Vasospasms" OR "Heart Arrest" OR "Heart Arrest" OR "Cardiac Arrest" OR "Asystole" OR Asystol* OR "Cardiopulmonary Arrest" OR "Atrioventricular Block*" OR "Heart Block*") NOT TI("veterinary" OR "rabbit" OR "rabbits" OR "animal" OR "animals" OR "mouse" OR "mice" OR "rodent" OR "rodents" OR "rat" OR "rats" OR "pig" OR "pigs" OR "porcine" OR "horse" OR "horses" OR "equine" OR "cow" OR "cows" OR "bovine" OR "goat" OR "goats" OR "sheep" OR "ovine" OR "canine" OR "dog" OR "dogs" OR "feline" OR "cat" OR "cats")) OR (AB("Sugammadex" OR "sugammadex" OR sugammadex* OR "Org 25969" OR "Bridion") AND AB("Bradycardia" OR "bradycardia" OR Bradycardia* OR "Bradyarrhythmia" OR Bradyarrhythm* OR "Heart Arrhythmia" OR "Arrhythmias" OR Arrhythm* OR "Coronary artery spasm" OR "Coronary Vasospasm" OR "Coronary Vasospasms" OR "Coronary Artery Vasospasm" OR "Coronary Artery Vasospasms" OR "Heart Arrest" OR "Heart Arrest" OR "Cardiac Arrest" OR "Asystole" OR Asystol* OR "Cardiopulmonary Arrest" OR "Atrioventricular Block*" OR "Heart Block*") NOT TI("veterinary" OR "rabbit" OR "rabbits" OR "animal" OR "animals" OR "mouse" OR "mice" OR "rodent" OR "rodents" OR "rat" OR "rats" OR "pig" OR "pigs" OR "porcine" OR "horse" OR "horses" OR "equine" OR "cow" OR "cows" OR "bovine" OR "goat" OR "goats" OR "sheep" OR "ovine" OR "canine" OR "dog" OR "dogs" OR "feline" OR "cat" OR "cats")) OR (TI("Sugammadex" OR "sugammadex" OR sugammadex* OR "Org 25969" OR "Bridion") AND TX("Bradycardia" OR "bradycardia" OR Bradycardia* OR "Bradyarrhythmia" OR Bradyarrhythm*) NOT TI("veterinary" OR "rabbit" OR "rabbits" OR "animal" OR "animals" OR "mouse" OR "mice" OR "rodent" OR "rodents" OR "rat" OR "rats" OR "pig" OR "pigs" OR "porcine" OR "horse" OR "horses" OR "equine" OR "cow" OR "cows" OR "bovine" OR "goat" OR "goats" OR "sheep" OR "ovine" OR "canine" OR "dog" OR "dogs" OR "feline" OR "cat" OR "cats"))