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DRUG SAFETY EVALUATION

Safety of sugammadex for reversal of neuromuscular block

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ABSTRACT

Introduction: Sugammadex is a modified cyclodextrin that is able to reverse neuromuscular block induced by aminosteroidal neuromuscular blocking drugs. Compared to reversal with neostigmine, it reverses neuromuscular block quicker and more predictable and without cholinergic side effects. However, there have been concerns about sugammadex ability to bind other drugs and its effects on QT interval and clotting times. In addition, sugammadex might induce hypersensitivity reactions more frequently than initially anticipated. This review summarizes current evidence with regard to these and other safety aspects of sugammadex.

Areas covered: This review provides an overview of the efficacy of sugammadex in various patient populations, evaluates potential interactions with other drugs and discusses adverse effects and reactions that have been reported in the literature.

Expert opinion: Sugammadex quickly reverses aminosteroid neuromuscular block with less side effects compared to neostigmine. As such, it has the potential to significantly reduce the incidence of residual neuromuscular block and to improve postoperative pulmonary outcome. Current safety concerns mainly focus on hypersensitivity reactions and cardiac arrhythmias. Although the absolute risk for these events is low, ongoing vigilance and research in this area are needed.

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1. Introduction

Muscle relaxants (neuromuscular blocking drugs – NMBDs) adjunct general anesthesia to facilitate endotracheal intubation and mechanical ventilation, and to optimize working conditions for the surgeon by reducing abdominal muscle tone [1–3]. However, as most NMBD has relatively long half-lives, a small amount of muscle relaxation may persist in the postoperative period (*i.e.* residual neuromuscular block – RNMB). Consequently, the use of NMBDs is associated with adverse respiratory events after anesthesia [4–6].

To reduce the risk of RNMB, anaesthesiologist are advised to use neuromuscular monitoring whenever an NMBD is used and exclusively remove the endotracheal tube when the *train-of-four-ratio* has recovered to at least 90% of baseline values (*ie*. TOF-ratio ≥0.9) [7]. If the TOF-ratio is less than 0.9 prior to extubation, reversal agents may be used to speed up the recovery of the neuromuscular block. Currently, two reversal methods exist. Acetylcholinesterase inhibitors (ACI; *eg*. neostigmine) are traditionally used to reverse shallow levels of residual neuromuscular block. These drugs temporarily increase the amount of acetylcholine in the neuromuscular junction which results in a competitive antagonism with the NMBD at the nicotinic acetylcholine receptor. Unfortunately, acetylcholinesterase inhibitors act slowly and are unpredictable in their reversal and they are unsuitable for the reversal of deep neuromuscular block [8,9]. In addition, they induce systemic cholinergic side-effects which necessitate the co-administration of an anticholinergic drug such as atropine.

In 2008 a new type of reversal agent became available after the clinical approval of the γ-cyclodextrin sugammadex in Europe. Sugammadex reverses neuromuscular block by permanent encapsulation of aminosteroidal NMBDs (*eg*. rocuronium or vecuronium) molecules in the plasma [10,11]. Multiple clinical studies have confirmed sugammadex' ability to quickly reverse both shallow and deep levels of aminosteroid neuromuscular block [12–19]. However, concerns about sugammadex induced hypersensitivity reactions have delayed approval in the US. Other potential safety concerns include its effects on QT interval and coagulation parameters. This review discusses these and other safety issues of sugammadex.

2. Review

2.1. Mechanism of action

Cyclodextrins are cone-shaped oligosaccharides that consist of six, seven or eight glucose monomers (α-, β- and γ-cyclodextrins). In pharmacology, they are widely used to increase the solubility of lipophilic medical compounds in water [20]. Sugammadex, originally known as ORG 25,969, is a modified variant of the natural γ-cyclodextrin and was developed as a solvent for rocuronium. By linkage of a side-chain to every 6th carbon-hydroxyl group, the length of the molecular cavity was increased to fit the rocuronium molecule. In addition, eight polar hydroxyl groups were placed at the end of each side-chain to create negatively charged outer-ends that are able to interact with positively charged nitrogen atoms of rocuronium (see Figure 1 and Box 1) [10,11,21]. One molecule of sugammadex is able to bind one molecule of the aminosteroid rocuronium. In addition, sugammadex binds other aminosteroidal NMBDs as well; binding affinity is highest for

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Box 1. Drug summary.

Drug name (generic): Sugammadex
Phase (for indication under discussion): Phase IV
Indication (specific to discussion): Reversal of aminosteroid induced NMB
Pharmacology description/mechanism of action: Cone-shaped encapsulating molecule capable of binding aminosteroidal NMBD with high affinity
Route of administration: Parenteral
Chemical structure: Octakis-(6-deoxy-6-S-mercaptoproprionyl- gamma-CD) sodium salt. See Figure 1.
Pivotal trial(s): Bom et al [11], Gijsenbergh et al [51], Staals et al [58].

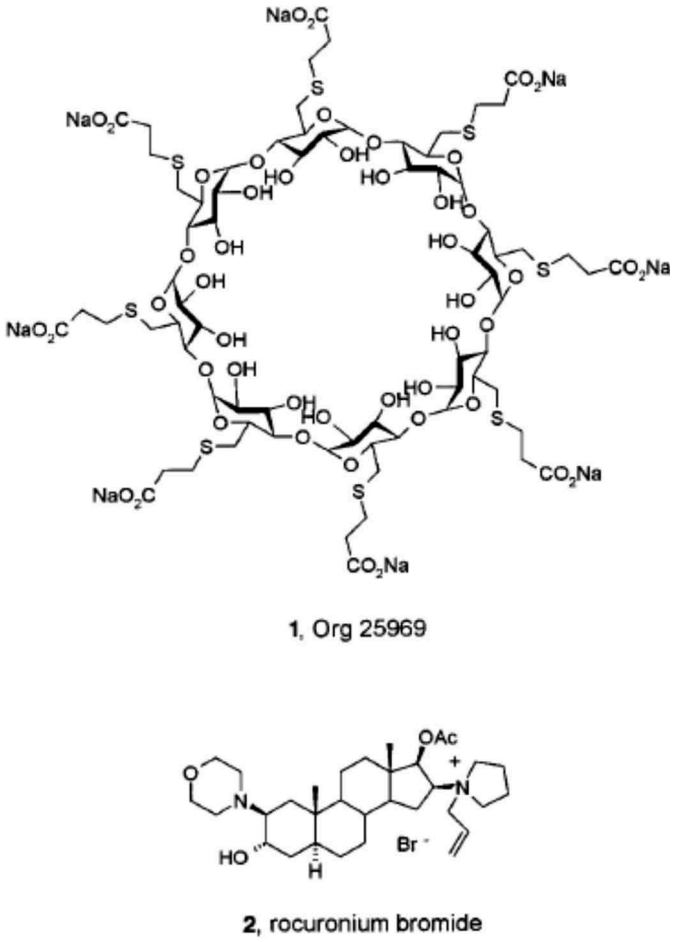

Figure 1. Schematic structures of sugammadex (Org 25969) and rocuronium. Reproduced with permission from John Wiley and Sons [11]. Copyright © 2002 WILEY-VCH Verlag GmbH, Weinheim, Fed. Rep. of Germany.

pipecuronium (Ka 161 × 10^6 M^{-1}) followed by rocuronium (Ka 25 × 10^6 M^{-1}), vecuronium (Ka 10 × 10^6 M^{-1}) and pancuronium (Ka 2.6 × 10^6 M^{-1}) [10,22,23].

Encapsulation of rocuronium by sugammadex effectively reduces the plasma levels of free, unbound rocuronium. This creates a negative gradient and causes rocuronium to diffuse out of the neuromuscular junction towards the plasma. Subsequently, these molecules become encapsulated by the remaining unbound fraction of sugammadex. Sugammadex also diffuses out of the plasma into the extracellular fluid compartment, encapsulating any unbound rocuronium it encounters. Both mechanisms result in the clearance of rocuronium molecules from the neuromuscular junction, liberating nicotinic acetylcholine receptors and restoring neuromuscular transmission [21]. Sugammadex should be administered in molar excess relative to the circulating NMBD to ensure that reversal is achieved in a quick and predictable fashion.

The hallmark effect of NMBDs is the inhibition of muscle contraction by a block of the postsynaptic (muscular type) nicotinic acetylcholine receptor (nAChR) at the neuromuscular junction. However, subtypes of the nAChR (*ie*. muscular and neuronal subtypes) are expressed on other cell types as well [24]. NMBD has shown to bind these nAChR subtypes with varying affinity [25]. Therefore, the effects of NMBDs are not restricted to the neuromuscular junction and may occur on other sites in the body where nAChRs are expressed [26,27]. For example, the peripheral chemoreflex to hypoxia is attenuated by NMBDs due to a direct block of the nAChR subtype expressed at the carotid bodies [26,28–30]. Sugammadex has shown to restore this reflex when used to reverse aminosteroid NMB [30].

2.2. Clinical applications and efficacy

In general, the dose of reversal agents depends on the degree of muscle relaxation at the moment of intended reversal. Therefore, a neuromuscular monitor device is necessary for adequate dosing of any reversal agent. Neuromuscular monitor devices deliver electrical stimuli to a peripheral nerve to elicit motor responses (twitches) in a corresponding muscle. NMBDs cause twitches to decrease in strength or to disappear. This allows for determination of the levels of NMB, which are defined as: intense NMB (no twitches in a train-of-four or post-tetanic-count), deep NMB (no twitches in a train-of-four and at least one twitch in a post-tetanic-count) and moderate NMB (at least one twitch in a train-of-four) [31]. Based on these definitions, the advised sugammadex dose for reversal of a moderate NMB is 2 mg/kg and sugammadex 4 mg/kg is advised for reversal of a deep NMB. With these doses, a TOF-ratio ≥0.9 is achieved in about 2 min (reversal of moderate NMB) and 1.6–3.3 min (deep NMB) [32]. In contrast, it takes on average 12.8 and 48.8 min to reach a TOF-ratio ≥0.9 when neostigmine 0.05–0.07 mg/kg is used for the reversal of a moderate and deep NMB, respectively [32]. In addition, the time range in which full recovery is achieved with neostigmine is much larger compared to reversal with sugammadex and outliers of delayed recovery are more common after neostigmine reversal [9,16]. Therefore, the use of neostigmine is limited to the reversal of a moderate NMB only [33].

There is no sugammadex dose recommendation for the routine reversal of an intense NMB. Intense NMB is usually only reached when a high-dose rocuronium (1.2 mg/kg) is administered as a part of a rapid sequence induction of anesthesia. However, should a subsequent respiratory emergency warrant urgent recovery to spontaneous ventilation in this situation, sugammadex at a dose of 16 mg/kg is recommended.

2.3. Residual neuromuscular block and recurrence of NMB

The use of NMBDs and reversal agents comes with the risk of insufficient reversal or the risk for re-occurrence of NMB after initial full reversal. Insufficient reversal is the consequence of

inappropriate administration of the reversal agent (*eg.* insufficient dose of the reversal agent, or reversal without the guidance of a neuromuscular monitor). Re-occurrence of NMB represents a pharmacokinetic phenomenon where the NMBD redistributes from a peripheral compartment and reinstitutes an NMB after initial full recovery. Both adverse events increase the risk of postoperative pulmonary complications [6]. Incomplete reversal and re-occurrence of NMB are traditionally associated with the use of acetylcholinesterase inhibitors, but sugammadex is no exception for that matter. Although the risk of both residual NMB and re-occurrence of NMB is negligible when sugammadex is dosed according to the manufacturers' recommendations, inappropriate dosing of sugammadex puts patients at risk for these adverse events [13,34,35]. A prospective, multicentre trial showed that reversal of a deep NMB with sugammadex 1 mg/kg (rather than 4 mg/kg) resulted in an incomplete reversal in 3 patients and re-occurrence of NMB 4 patients out of a total of 56 patients [34]. Re-occurrence of neuromuscular block was observed in obese patients following deep NMB and reversal with relatively low sugammadex doses (0.5–1.7 mg/kg). [35,36] Finally, patients that have received a prolonged infusion of rocuronium on the ICU may behave differently as compared to the standard anesthesia population and may develop recurrence of NMB despite adequate sugammadex dosing [37].

Neuromuscular monitoring is essential to ensure sugammadex is adequately dosed and to prevent inadvertent extubation at a TOF-ratio <0.9. If neuromuscular monitoring is omitted, both inappropriate dosing and too early extubation may occur. Three studies reported an incidence of RNMB of 3.8–4.3% when sugammadex was dosed without the guidance of a neuromuscular monitor [38–40].

Despite these evident risks, clinicians still seek ways to justify the use of reduced sugammadex doses in order to lower costs. In two studies (total *n*= 188), the efficacy of various low doses of sugammadex for the reversal of a shallow NMB was investigated [41,42]. Sugammadex doses of 0.49 and 0.22 mg/kg were calculated to be sufficient to reverse a TOF-ratio of 0.2 and 0.5, respectively, to a TOF-ratio of 0.9 within 5 min [41,42]. No cases of re-occurrence of NMB were reported in these studies. Finally, a small study compared sugammadex 4.0 mg/kg with a combination of sugammadex 2.0 mg/kg and neostigmine 50 µg/kg for reversal of a deep NMB in 28 patients. Both groups achieved a TOF-ratio ≥0.9 within 10 min after the reversal (mean time 181 ± 97 vs. 228 ± 84 sec; NS). Evidently, the use of the sugammadex neostigmine combination for reversal of a deep NMB in this study is off-label and additional safety data are needed before this strategy deserves a recommendation.

2.4. Special considerations

2.4.1. Elderly

In general, elderly patients are more susceptible to the adverse effects of residual NMB and spontaneous recovery of NMB is slower compared to younger patients [43–45]. A multicentre, phase III study investigated the influence of age on the safety, efficacy, and pharmacokinetics of sugammadex reversal of a rocuronium induced NMB and found reversal times to be modestly increased in elderly compared to patients aged <65 years (mean time 2.9 vs. 2.3 min) [46]. Sugammadex was well tolerated, and no cases of recurrence of NMB were described.

2.4.2. Pediatrics

Data from phase II studies have shown that sugammadex is equally effective and safe in the pediatric population (neonates, infants, children, and adolescents) as in adults [47,48]. This was confirmed by a meta-analysis on 10 studies (*n* = 575) and by a recently published retrospective cohort study (*n*= 968) [49,50]. Additionally, these studies found that sugammadex reduced the risk of bradycardia when compared to the use of neostigmine combined with atropine. No significant difference in the occurrence of other adverse events, such as bronchospasm or postoperative nausea and vomiting, was found [49,50]

2.4.3. Morbid obese (body mass index >40 kg/m^2)

Obese patients have an increased proportion of fat and lean body mass relative to their total body weight. Sugammadex is known to primarily distribute to the extracellular fluid, as it is unable to cross cell membranes [51]. Hence, it would make sense to dose sugammadex based on ideal or lean, rather than total body weight in obese patients. This was studied by Van Lancker et al., who compared the efficacy of sugammadex dosing based on ideal body weight (IBW) versus total body weight (TBW) for reversal of a moderate NMB in patients with a BMI > 40 kg/m^2. IBW based sugammadex dosing was sufficient for all patients to reach a TOF-ratio of 0.9 or higher in 189 ± 84 s, although dosing based on IBW +40% or TBW resulted in faster recovery times (112.5 ± 30.3 and 128.8 ± 47.0 s, respectively). No cases of (clinical) recurrence of NMB were noted [52]. Others have found similar results [53,54]. In contrast, a study by Llaurado et al. concluded that sugammadex based on IBW was insufficient for reversal of both moderate and deep NMB [55]. However, this study was criticized for methodological short comings (*eg.* inappropriate sugammadex dose and allowance of a second sugammadex dose if the TOF-ratio had not reached 0.9 within 2 min), restricting any definitive conclusions [56]. Similarly, Loupec et al. found that sugammadex 4 mg/kg dosed on IBW was possible in most, but not all patients for reversal of deep NMB within 10 min (success rate 93%) [57]. Based on these data, and on the fact that sugammadex is well tolerated, there are strong arguments for sugammadex to be dosed on TBW rather than IBW estimates, in order to obtain quick and predictable recovery in all patients of this vulnerable population.

2.4.4. Renal failure

Sugammadex and the sugammadex-rocuronium complex are exclusively excreted unchanged via the kidneys [51]. As such, sugammadex (both complexed and unbound) excretion is prolonged in patients with renal failure [58]. Concerns regarding the prolonged presence of sugammadex-rocuronium complexes and the paucity of safety data in these patients have led to the recommendation that sugammadex should not be used in patients with a glomerular filtration rate of less than 30 mL/min. Nevertheless, current data suggest that sugammadex can safely be used in patients with end-stage renal disease; no cases of recurrence of NMB have been described as of yet, bearing in mind that current safety data are limited to the first 48 h after sugammadex administration [58,59]. The

rocuronium-sugammadex complex can be eliminated by hemodialysis, but only through a high-flux filter membrane [58,60]. Finally, it is important to note that reversal times in patients with renal disease may be prolonged [61,62], although this is not a consistent finding [59]. Again, neuromuscular monitoring is mandatory to detect these outliers.

2.4.5. Administration of NMBDs after sugammadex administration

Occasionally, patients need to undergo a (second) surgical procedure shortly after the first one has finished. In case sugammadex was used for reversal in the prior procedure, obtaining an NMB in the second procedure needs some consideration as free, unbound sugammadex may still be circulating. If physicians intend to use an aminosteroidal NMBD in this situation, a distinct dose recommendation by the manufacturer should be followed. During the first 4 h after sugammadex administration, a dose of rocuronium 1.2 mg/kg is recommended [63]. This has shown to achieve an NMB within several minutes (mean onset time of 3.1 min, range 1.92–4.72) [64]. When 4 h have passed since the prior sugammadex administration, the normal dose of rocuronium (0.6 mg/kg) or vecuronium (0.1 mg/kg) is advised [63]. Importantly, the use of aminosteroidal NMBDs is not recommended in the first 5 min after sugammadex administration. In addition, patients with mild of moderate renal impairment should receive rocuronium 1.2 mg/kg during the first 24 h after sugammadex administration [63]. Alternatively, physicians may use benzylisoquinoline NMBDs or succinylcholine instead of aminosteroidal NMBDs to obtain an NMB in these situations.

2.5. Drug interactions

Cyclodextrins are theoretically capable of interacting with other drugs besides aminosteroidal NMBDs. This could result in dissociation of the NMBD from sugammadex, resulting in prolonged reversal times or recurrence of neuromuscular block. This was investigated by Zwiers et al., who developed a pharmacokinetic-pharmacodynamic model that took into account the binding affinity for sugammadex of NMBDs and 300 other commonly used drugs [65]. Their model indicated that toremifene and fusidic acid have a displacement potential, albeit in concentrations that are unlikely to be achieved during routine administration of these drugs [65]. In addition, flucloxacillin was found to be able to interact with sugammadex, however a subsequent clinical study could not confirm a significant displacement interaction [66]. The model of Zwiers et al. also indicated that corticosteroids were unlikely to interact with sugammadex [65]. This contrasted with *in vitro* findings, indicating that high-dose dexamethasone could reduce the efficacy of sugammadex in a human muscle cell model [67], but agrees with a human study which found no effect of sugammadex 4 mg/kg on serum cortisol levels [68].

Finally, the model by Zwiers et al. predicted that 34% of etonogestrel (a progestagen metabolite) could be captured by sugammadex, albeit under very conservative model assumptions [65]. Nevertheless, the sugammadex product information advises additional anti-conceptive methods to be used when sugammadex is administered [63]. Depending on the type of hormonal contraceptives, either additional non-hormonal contraceptive methods should be used for 7 days after sugammadex administration, or the contraceptive package leaflet instructions should be followed as if a daily dose was missed [63]. However, the true effects of sugammadex on progestogen levels *in vivo* remain speculative. Progestogen has a much higher affinity for sex hormone binding globulin (Ka 8.8 megaMol^{-1}) and transcortin (Ka 24 megaMol^{-1}) than for sugammadex (Ka 1.5 megaMol^{-1}) [69]. Indeed, a human study found that the effect of sugammadex 4 mg/kg on serum progesterone or other steroidal hormone levels was not clinically relevant [68].

2.6. Adverse events associated with sugammadex use

2.6.1. Anaphylaxis & hypersensitivity

Incidence of hypersensitivity and anaphylaxis is a major concern with the introduction of any new medical agent. Recently, two studies reported alarming incidences of sugammadex induced hypersensitivity and anaphylaxis [70,71]. Incidences of hypersensitivity were found to be 0.7% and 6.6% after sugammadex 4 mg/kg and 4.7% and 9.5% after sugammadex 16 mg/kg. Additionally, each study diagnosed one case of anaphylaxis after sugammadex 16 mg/kg. Combining these data would yield an incidence of hypersensitivity of 5% (32/597) and an incidence of anaphylaxis of 0.3% (2/597) after any dose of sugammadex [72]. Additionally, a recent retrospective study in children observed an incidence of anaphylaxis of 0.1% [50]. These high incidences of hypersensitivity and anaphylaxis contradict with other reported incidences, which are generally much lower. In Japan, 95 cases of sugammadex-related hypersensitivity reactions were reported between 2010 and 2013; 78 patients filled the criteria for anaphylaxis. Based on the estimated number of patients that had received sugammadex in the study period, an incidence of 1:34,483 was calculated [73]. A global survey among anesthesia providers between March 2016 and May 2017 yielded an estimated incidence of anaphylaxis of 1:1,000–1:20,000 [74]. Similar estimations were reported in a 3-year retrospective Japanese survey and in the 2015 FDA briefing report for sugammadex [75].

Currently, the exact mechanism of these hypersensitivity reactions remains unknown. Patients can easily be sensitized by cyclodextrins as these are present in food and cosmetic products. However, studies by de Kam and Min et al. neither could establish a correlation between hypersensitivity and serum tryptase levels, skin testing, or sugammadex specific Ig-E or Ig-G antibodies [70,71]. Establishing hypersensitivity diagnosis can be troublesome, as many tests lack high sensitivity and specificity for hypersensitivity. However, in a case series, skin tests have been used to confirm sugammadex related hypersensitivity [76].

Apart from hypersensitivity reactions to either sugammadex or rocuronium, it has been proposed that the rocuronium-sugammadex complex in itself is able to provoke an allergic reaction due to a change of its immunological properties [77,78]. Finally, the administration of sugammadex in the treatment of rocuronium induced anaphylaxis remains unclear. In several case, sugammadex appeared to be beneficial for the treatment of rocuronium induced anaphylaxis [79,80]. However,

other cases report no improvement by sugammadex in the treatment of rocuronium induced anaphylaxis [79,81,82].

2.6.2. Cardiac arrhythmias & QT interval prolongation

As a part of safety evaluation, multiple phase I and II studies have investigated the effect of sugammadex on QTc interval prolongation. Data from anesthetized individuals showed that sugammadex did not induce clinically relevant QTc prolongation, even in doses far above the recommended doses (up to 32 mg/kg) [51,83–85]. In contrast, findings from other studies that applied sugammadex during general anesthesia showed slightly higher QTc values [15,17]. However, interpretation of these data is not straightforward as many anesthetic agents by themselves produce QT interval changes. To date, multiple studies have confirmed the safety of sugammadex under both propofol and sevoflurane anesthesia, and in patients with and without cardiac disease, all showing that sugammadex does not substantially prolong QTc in routine daily anesthetic practice [86–89].

Information from the manufacturer also indicate that sugammadex can induce a wide variety of cardiac arrhythmias (*ie.* atrial or ventricular fibrillation, atrioventricular and ST segment changes), however the most notable arrhythmia is bradycardia which may lead to asystole in severe cases. Compared to neostigmine, however, the overall incidence of bradycardia in both children and adults appears to be lower with sugammadex [50,90].

2.6.3. Anticoagulant effects

Sugammadex is generally considered not to have any biological activity. However, in healthy volunteers and surgical patients, sugammadex was shown to increase activated partial thromboplastin time (aPTT) and prothrombin time (PT) after 4 and 16 mg/kg sugammadex administration [91,92]. A follow-up study found that sugammadex affects various coagulation assays through binding to phospholipids present in such assays [93]. The authors concluded that the increased PT and aPTT are likely to be an *in vitro* artifact [93]. Two clinical studies confirmed that sugammadex did not result in clinically significant bleeding excess in an orthopedic and ENT surgical populations [92,94].

3. Conclusion

Sugammadex is able to quickly and predictably reverse any depth of aminosteroidal neuromuscular block. It reduces the incidence of residual neuromuscular block, especially when compared to acetylcholinesterase inhibitors, but effects on major outcomes have yet to be established. Safety concerns mainly focus on hypersensitivity reactions and cardiac arrhythmias, which occasionally result in life-threating events. Although the absolute risk for such events is probably low, ongoing vigilance and research in this area are needed.

4. Expert opinion

With the introduction of sugammadex, a new way of neuromuscular reversal became available that differs radically from reversal with acetylcholinesterase inhibitors. By encapsulating aminosteroidal neuromuscular blocking drugs (NMBD), sugammadex is able to reverse any depth of neuromuscular block in a short period of time. *In vitro* indications that sugammadex is able to bind to other (i.e. non-NMBD) steroidal agents are probably not relevant *in vivo*. Additionally, the effects of sugammadex on the QT-interval or clotting time do not appear to be of clinical significance. However, there are tenacious concerns with the use of sugammadex, of which the most important are the recently reported high incidence of hypersensitivity reactions [50,70,71], and adverse cardio-vascular events such as bradycardia and hemodynamic collapse [95,96]. Although the presentation of these conditions sometimes overlap, the involved mechanisms remain unknown.

Post-marketing data of sugammadex associated adverse events are however reassuring. In the Netherlands, 13 cases of a severe adverse event have been reported to the Netherlands Pharmacovigilance Centre Lareb between 2011 and November 2017. This included one case with bradycardia and 5 cases with anaphylaxis [97]. Data on mortality are not available. The 2015 FDA briefing document of sugammadex reports 273 cases of anaphylaxis among 11.5 million sugammadex exposures of which 4 were fatal [98]. In addition, fatal outcome related to cardiac arrhythmias was reported in 3 cases and related to other causes in 6 patients. The document concludes that sugammadex does not substantially elevate the perioperative risk for anaphylaxis (estimated to be 24 per 100.000) or fatal outcome (estimated to be 1.1 per 100.000). The estimated incidence for anaphylaxis in this document agrees with recently reported retrospective and survey based incidences [74,75], and aligns sugammadex to other routinely administered high-risk agents [99]. Finally, a recent Cochrane meta-analysis reported an equal risk for serious adverse events for both sugammadex and neostigmine (<1%), but a superior overall risk-benefit profile for sugammadex [90]. We contend that sugammadex is safe to use and that only on rare occasions it may induce life-threatening reactions.

It is our opinion that sugammadex offers advantages in the perioperative setting that outweigh the previous stated concerns, especially when compared to its alternative neostigmine. Sugammadex significantly reduces the incidence of residual neuromuscular block [100], provided that objective neuromuscular monitoring is applied and sugammadex is properly dosed [38–40]. This is pivotal, as incidences of RNMB and the associated pulmonary complications are traditionally substantial and have not shown any improvement over the past decades [101]. Neostigmine has clearly failed to make a significant difference in those years. Finally, there are indications that neostigmine has direct detrimental effects that might worsen, rather than improve respiratory outcome after anesthesia [102–104], although this remains subject of debate [105].

Achievement of predictable, full neuromuscular recovery with sugammadex, would logically translate to fewer postoperative adverse respiratory events. Evidence from retrospective and small prospective studies suggests that this could be true [38,100,106], but a recently published large multi-center randomized controlled trial did not confirm this [107]. This trial, however, suffered from methodological flaws, including suboptimal neuromuscular clinical care and suboptimal dosing of reversal agents, which restricts conclusions [108–110]. In

the end, postoperative complications are not solely dependent on the type of reversal agent, but on all aspects that are considered to be part of good clinical practice. This entails the use of neuromuscular monitoring and respecting an adequate TOF-ratio threshold for extubation.

As sugammadex is able to quickly reverse any depth of aminosteroid neuromuscular block, it opened the door for the clinical application of a high-dose muscle relaxant anesthetic technique aimed at maintaining a deep neuromuscular block throughout the surgical procedure. Maintaining a deep neuromuscular block improves surgical working conditions in selected laparoscopic procedures [1,2]. Whether this technique is able to improve patient outcome should be assessed in future research.

Declaration of interest

M Boon, A Dahan, and CH Martini have received consultancy and/or speaker fees from MSD. A Bom is a former Senior Research Fellow of the Department of Pharmacology, MSD, Newhouse Scotland and is the inventor of the concept behind sugammadex. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

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