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ADIS DRUG EVALUATION

Sugammadex: A Review of Neuromuscular Blockade Reversal

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Abstract Sugammadex (Bridion®) is a modified γ-cyclodextrin that reverses the effect of the steroidal nondepolarizing neuromuscular blocking agents rocuronium and vecuronium. Intravenous sugammadex resulted in rapid, predictable recovery from moderate and deep neuromuscular blockade in patients undergoing surgery who received rocuronium or vecuronium. Recovery from moderate neuromuscular blockade was significantly faster with sugammadex 2 mg/kg than with neostigmine, and recovery from deep neuromuscular blockade was significantly faster with sugammadex 4 mg/kg than with neostigmine or spontaneous recovery. In addition, recovery from neuromuscular blockade was significantly faster when sugammadex 16 mg/kg was administered 3 min after rocuronium than when patients spontaneously recovered from succinylcholine. Sugammadex also demonstrated efficacy in various special patient populations, including patients with pulmonary disease, cardiac disease, hepatic dysfunction or myasthenia gravis and morbidly obese patients. Intravenous sugammadex was generally well tolerated. In conclusion, sugammadex is an important option for the rapid reversal of rocuronium- or vecuronium-induced neuromuscular blockade.

Sugammadex: clinical considerations in neuromuscular blockade reversal

Modified γ-cyclodextrin that reverses the effect of rocuronium and vecuronium in a dose-dependent manner

Rapidly and predictably reverses moderate and deep neuromuscular blockade

Effective in the immediate reversal of neuromuscular blockade

Generally well tolerated

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1 Introduction

The use of neuromuscular blocking agents (NMBAs) during surgery facilitates tracheal intubation, protects patients from vocal cord injury and improves surgical conditions by suppressing voluntary or reflex skeletal muscle movements [1]. Historically, acetylcholinesterase (AChE) inhibitors (e.g. neostigmine, pyridostigmine, edrophonium) have been used to reverse NMBA action [2]. By inhibiting the breakdown of acetylcholine, AChE inhibitors increase the amount of acetylcholine available to compete with the NMBA at the neuromuscular junction, leading to an

acceleration of the recovery of skeletal muscle function [1, 2]. However, AChE inhibitors have limited efficacy in reversing deep neuromuscular blockade, reflecting the fact that the speed of recovery of neuromuscular function with these agents is unpredictable and a ceiling effect is reached when AChE inhibition is near 100 % [3]. Moreover, there is potential for residual neuromuscular blockade with AChE inhibitors and coadministration of anticholinergics is required to minimize muscarinic adverse effects (e.g. bradycardia, hypersalivation) [2, 4]. Thus, there is a need for new reversal agents without these limitations.

Sugammadex (Bridion®) has a novel mechanism of action and was approved in the EU in 2008 for the reversal of rocuronium- and vecuronium-induced neuromuscular blockade [5]. Subsequently, sugammadex has been approved in numerous countries worldwide, and was recently approved in the USA [6].

This narrative review discusses the therapeutic efficacy, safety and tolerability of sugammadex for the reversal of neuromuscular blockade induced by rocuronium or vecuronium in adults undergoing surgery, as well as summarizing its pharmacological properties. The use of sugammadex in paediatric patients is beyond the scope of this review.

2 Pharmacodynamic Properties of Sugammadex

Sugammadex is a modified γ-cyclodextrin that rapidly reverses the effect of the steroidal nondepolarizing NMBAs rocuronium and vecuronium [1, 7]. Sugammadex forms a stable, inactive 1:1 complex with rocuronium or vecuronium; this reduces the amount of free NMBA that is available to bind to nicotinic acetylcholine receptors at the neuromuscular junction, resulting in reversal of neuromuscular blockade [1, 7].

In healthy anaesthetized volunteers, a single intravenous dose of sugammadex 1–8 mg/kg rapidly reversed neuromuscular blockade induced by rocuronium 0.6 mg/kg in a dose-dependent manner [8]. The degree of residual neuromuscular blockade at the time of sugammadex administration influenced the speed of reversal of rocuronium-induced neuromuscular blockade [9]. The choice of anaesthetic agent (propofol or sevoflurane) did not affect the ability of sugammadex 2 [10] or 4 [11] mg/kg to reverse rocuronium-induced neuromuscular blockade. The efficacy of sugammadex in reversing rocuronium- or vecuronium-induced neuromuscular blockade in patients undergoing surgery is discussed in Sect. 4.

Sugammadex 2 [12] or 2–16 [13] mg/kg did not affect the depth of anaesthesia (propofol and remifentanil [12] or thiopental, fentanyl and sevoflurane [13] anaesthesia), according to bispectral index (BIS) or Entropy™ values [12, 13]. While a significant ($p < 0.05$ vs. baseline) increase in BIS values was seen following administration of sugammadex 4 mg/kg to patients with high electromyographic activity during stable propofol and remifentanil anaesthesia, this reflected muscle activity reappearance, rather than consciousness [14].

Although transient increases in the activated partial thromboplastin time (aPTT) and international normalized ratio (INR) were reported following administration of sugammadex 4 [15, 16] or 16 [15] mg/kg to healthy volunteers [15] or patients undergoing orthopaedic surgery who were receiving thromboprophylaxis with low molecular weight heparin and/or antiplatelet agents [16], these change were not considered clinically relevant [15, 16]. Moreover, sugammadex 4 mg/kg did not have clinically relevant effects on platelet aggregation, bleeding time or the aPTT in healthy volunteers receiving daily aspirin [17], and sugammadex 4 or 16 mg/kg did not have clinically relevant effects on anti-factor Xa activity or the aPTT in healthy volunteers who had received pretreatment with enoxaparin sodium or unfractionated heparin [18]. No prolongation of the aPTT or prothrombin time occurred in patients undergoing laparotomy who received sugammadex 2 or 4 mg/kg [19]. Sugammadex was not associated with an increased risk of bleeding in patients undergoing orthopaedic surgery [16].

Patients with New York Heart Association class II–IV heart failure undergoing a cardiac procedure remained haemodynamically stable during reversal of neuromuscular blockade with sugammadex 2 mg/kg [20]. However, recovery times appeared longer in patients with heart failure than in healthy younger patients [20], most likely reflecting reduced cardiac output and a slower circulation time for sugammadex.

Administration of an intravenous therapeutic dose (4 mg/kg) of sugammadex alone [21, 22] or a supratherapeutic dose (32 mg/kg) of sugammadex alone [21, 22] or in combination with rocuronium or vecuronium [21] was not associated with clinically relevant prolongation of the corrected QT (QTc) interval, according to the results of thorough QTc studies. Moreover, when sugammadex 4 mg/kg was administered to healthy subjects in whom anaesthesia was maintained with propofol or sevoflurane (which are associated with QTc prolongation), sugammadex did not result in further clinically relevant prolongation of the QTc interval [23].

Various drugs besides rocuronium and vecuronium have high binding affinities for sugammadex, meaning that displacement of rocuronium or vecuronium from the complex with sugammadex and recurrence of neuromuscular blockade could potentially occur [24]. Screening identified three drugs (toremifene, flucloxacillin and fusidic acid) with potential for displacement interactions with

sugammadex [24]. Prescribing information states that recovery from neuromuscular blockade could be delayed in patients who receive toremifene on the day of surgery [6, 25]. A study in healthy anaesthetized volunteers undergoing reversal of rocuronium- or vecuronium-induced neuromuscular blockade with sugammadex 2 mg/kg found that flucloxacillin did not result in recurrence of neuromuscular blockade [26].

Progestogens may also bind to sugammadex, thereby decreasing progestogen exposure [6]. An additional, non-hormonal contraceptive method or back-up method of contraception should be used for the next 7 days if an oral contraceptive containing an estrogen or progestogen is taken on the same day as sugammadex [6], and in patients using non-oral hormonal contraceptives [6, 25].

3 Pharmacokinetic Properties of Sugammadex

Intravenous bolus doses of sugammadex 1–16 mg/kg demonstrated linear pharmacokinetics [6, 8, 25, 27]. Sugammadex had an observed volume of distribution at steady state of ≈11–14 L in adults with normal renal function [6, 25]. In vitro, no binding was seen between plasma proteins or erythrocytes and sugammadex or the sugammadex-rocuronium complex [6, 25].

No metabolites of sugammadex were detected in clinical studies [6, 25]. Sugammadex is predominantly excreted renally as unchanged drug [6]; excretion is rapid, with 92 % of radioactivity recovered within 24 h following administration of radiolabelled sugammadex [28]. In adult anaesthetized patients with normal renal function, sugammadex had an estimated plasma clearance of ≈88 mL/min and an elimination half-life ($t_{½}$) of ≈2 h [6, 25].

As expected, given that sugammadex is renally excreted, sugammadex exposure was increased in patients with moderate or severe renal impairment [6, 25, 29]. In patients with mild, moderate or severe renal impairment, sugammadex had a $t_{½}$ of 4, 6 and 19 h, respectively [6]. No dose adjustment is needed in patients with mild to moderate renal impairment [6, 25], although the use of sugammadex in patients with severe renal impairment (creatinine clearance <30 mL/min) is not recommended [6, 25].

No sugammadex dose adjustment is needed in patients with pulmonary or cardiac disease [6], or in patients with hepatic impairment [6, 25] (see also Sect. 4.4), although the EU summary of product characteristics recommends caution in patients with severe hepatic impairment and in patients with hepatic impairment and coagulopathy [25], and the US prescribing information recommends caution in patients with hepatic impairment who have coagulopathy or severe oedema [6].

Sugammadex clearance was ≈50 % lower in elderly patients aged ≥75 years than in patients aged 18–64 years [30]. However, no dose adjustment is recommended in elderly patients with normal organ function [6, 25], although, given that renal function may be decreased in the elderly, the US prescribing information states that the sugammadex dose should be selected with care and it may be useful to monitor renal function in these patients [6].

No clinically relevant differences in sugammadex pharmacokinetics were seen between healthy Japanese and Caucasian subjects [6, 25]. The plasma concentration-time profile of sugammadex in Chinese healthy volunteers was similar to that observed in Caucasian and Japanese subjects [31].

No clinically relevant relationship between the clearance or volume of distribution of sugammadex and bodyweight was seen in adult or elderly patients [25]. The sugammadex dose should be based on actual bodyweight [6, 25].

4 Therapeutic Efficacy of Sugammadex

The efficacy of intravenous sugammadex in the reversal of neuromuscular blockade was initially shown in dose-finding studies. For example, administration of sugammadex at reappearance of the second twitch (T_2) of train-of-four (TOF) stimulation resulted in rapid, dose-dependent reversal of moderate neuromuscular blockade induced by rocuronium [27, 32–35], vecuronium [27, 34, 35] or pipecuronium [36]. Administration of sugammadex at a post-tetanic count (PTC) of 1–2 also reversed deep neuromuscular blockade induced by rocuronium [37–39] or vecuronium [37, 39] in a dose-dependent manner. Early reversal of profound neuromuscular blockade occurred in a dose-dependent manner when sugammadex was administered 3 [40, 41], 5 [41, 42] or 15 min [40, 41] after rocuronium.

Results of these dose-finding trials will not be discussed further. Rather, this section focuses on randomized controlled trials that administered sugammadex as recommended in the US [6] and EU [25] prescribing information [i.e. 2 mg/kg at the reappearance of T_2 after discontinuation of rocuronium or vecuronium, 4 mg/kg at 1–2 PTCs after discontinuation of rocuronium or vecuronium, or 16 mg/kg for immediate reversal of neuromuscular blockade soon (≈3 min) after administration of rocuronium] (see Sect. 6). Neuromuscular function was monitored with acceleromyography at the adductor pollicis muscle using TOF-Watch SX®.

4.1 Reversal of Moderate Neuromuscular Blockade

Randomized, multicentre trials of safety assessor-blind [43–47] or double-blind [48] design compared the efficacy

of sugammadex with that of neostigmine administered at the reappearance of T_2 for the reversal of moderate neuromuscular blockade. The trials included adults who were American Society of Anesthesiologists (ASA) physical status I–III [43–47] or I–IV [48] and undergoing surgery under general anaesthesia induced by propofol and maintained by sevoflurane [43, 45, 47, 48], desflurane [48] or propofol [44, 46], with opioids also permitted. Patients received intravenous sugammadex 2 mg/kg or neostigmine 50 μg/kg plus glycopyrrolate [43–45, 47, 48] or atropine [46]. Patients receiving sugammadex underwent neuromuscular blockade with rocuronium [43–46, 48] or vecuronium [47], and patients receiving neostigmine underwent neuromuscular blockade with rocuronium [43, 45, 46, 48], vecuronium [47] or cisatracurium [44]. Primary endpoints were the time to recovery of the TOF ratio to 0.9 assessed from the start of administration of the reversal agent [43–47] or from the loss of visual fade in the TOF response [48]. Efficacy was assessed in the modified intent-to-treat (ITT) population [43–48].

Recovery of neuromuscular function from moderate neuromuscular blockade was significantly faster with sugammadex than with neostigmine. The geometric mean time from administration of the reversal agent until recovery of the TOF ratio to 0.9 was significantly shorter with sugammadex than with neostigmine [43–47], including in Korean [45] and Chinese [46] patients (Table 1). The geometric mean time from administration of the reversal agent until recovery of the TOF ratio to 0.8 or 0.7 was also significantly shorter with sugammadex than with neostigmine (Table 1) [43–45, 47].

Recovery times were less variable with sugammadex than with neostigmine. A TOF ratio of 0.9 had been reached by 98 % of sugammadex recipients versus 11 % of neostigmine recipients 5 min after administration of the reversal agent in one study; it took 101 min for a TOF ratio of 0.9 to be reached by 98 % of neostigmine recipients [43]. Approximately 89 % of Korean patients reached a TOF ratio of 0.9 in <3 min with sugammadex versus 38.5 min with neostigmine [45]. Within 3 min of

Table 1 Efficacy of intravenous sugammadex 2 mg/kg vs. neostigmine 50 μg/kg administered for the reversal of moderate neuromuscular blockade at the reappearance of T_2

Study (study name/patient group)	NMBA	Reversal agent	No. of pts	Mean[a] time to recovery of TOF ratio (median; range) [min]		
				to 0.9[b]	to 0.8	to 0.7
Blobner et al. [43]	ROC[c]	SUG	48	1.5** (1.4; 0.9–5.4)	1.2** (1.2; 0.9–3.4)	1.1** (1.0; 0.7–2.7)
(AURORA)	ROC[c]	NEO[d]	48	18.6 (18.5; 3.7–106.9)	10.8 (9.8; 2.7–67.9)	7.2 (6.2; 2.4–41.1)
Flockton et al.	ROC[c]	SUG	34	1.9** (1.9; 0.7–6.4)	1.6** (1.5; 0.7–3.4)	1.4** (1.2; 0.7–2.9)
[44] (CRYSTAL)	CIS[e]	NEO[d]	39	9.0 (7.3; 4.2–28.2)	6.5 (5.9; 3.2–15.6)	5.1 (4.7; 2.4–10.9)
Illman et al. [48]	ROC[c]	SUG	23	0.3* (NR; 0.0–1.0)	0.1* (NR; 0.0–0.5)	0.0* (NR; 0.0–0.3)
	ROC[c]	NEO[d]	24	10.3 (NR; 1.3–26.0)	7.1 (NR; 1.0–20.5)	4.6 (NR; 0.3–10.3)
Woo et al. [45]	ROC[c]	SUG	59	1.8** (NR; 1.0–8.3)	1.4** (NR; 0.7–4.1)	1.2** (NR; 0.6–3.0)
(Korean pts)	ROC[c]	NEO[d]	59	14.8 (NR; 4.1–80.6)	10.7 (NR; 3.3–42.3)	7.1 (NR; 2.8–33.4)
Wu et al. [46]	ROC[c]	SUG	119	1.6** (NR; 0.6–6.2)	1.3[f] (NR; 0.6–2.8)	1.1[f] (NR; 0.4–2.1)
(Chinese pts)	ROC[c]	NEO[d]	111	9.1 (NR; 2.7–60.4)	6.0[f] (NR; 2.2–59.6)	4.4[f] (NR; 1.7–32.4)
Wu et al. [46]	ROC[c]	SUG	29	1.4** (NR; 0.8–2.0)	1.2[f] (NR; 0.8–1.7)	1.0[f] (NR; 0.6–1.7)
(Caucasian pts)	ROC[c]	NEO[d]	30	6.7 (NR; 3.0–31.4)	4.6[f] (NR; 2.4–14.1)	3.4[f] (NR; 1.9–7.9)
Khuenl-Brady et	VEC[g]	SUG	48	2.7** (2.1; 1.2–64.2)	1.9** (1.7; 1.0–4.3)	1.6** (1.4; 0.7–3.4)
al. [47] (AURORA)	VEC[g]	NEO[d]	45	17.9 (21.9; 2.9–76.2)	10.8 (13.6; 2.2–59.1)	6.4 (5.2; 1.9–54.3)

CIS cisatracurium, *NEO* neostigmine, *NMBA* neuromuscular blocking agent, *NR* not reported, *pts* patients, *ROC* rocuronium, *SUG* sugammadex, *TOF* train of four, T_2 second twitch of TOF stimulation, *VEC* vecuronium

* $p < 0.001$, ** $p < 0.0001$ vs. NEO

[a] Assessed from the start of administration of the reversal agent [43–47] or from the loss of visual fade in the TOF response [48]. Geometric mean [43–47] or mean [48] values

[b] Primary endpoint

[c] Bolus dose of ROC 0.6 mg/kg followed by maintenance with ROC 0.1–0.2 mg/kg as needed [43–46], or ROC 0.6–1 mg/kg followed by maintenance with ROC 5–10 mg as needed [48]

[d] Glycopyrrolate 10 μg/kg [43–45, 47, 48] or atropine 10–20 μg/kg [46] was coadministered with NEO

[e] Bolus dose of CIS 0.15 mg/kg followed by up to two doses of CIS 0.03 mg/kg

[f] Statistical analysis not reported

[g] Bolus dose of VEC 0.1 mg/kg followed by maintenance with VEC 0.02–0.03 mg/kg as needed

administration of sugammadex and neostigmine, 91 and 2 % of Chinese patients reached a TOF ratio of 0.9 [46]. There was no clinical evidence of residual neuromuscular blockade or recurrence of neuromuscular blockade in sugammadex or neostigmine recipients [43, 47].

The mean time from the loss of visual fade until recovery of the TOF ratio to 0.9 (i.e. the potentially unsafe period of recovery) was significantly shorter with sugammadex than with neostigmine (Table 1) [48]. Significantly ($p < 0.001$) shorter mean times from the loss of visual fade until recovery of the TOF ratio to 0.8 or 0.7 (Table 1) and from administration of the reversal agent until recovery of the TOF ratio to 0.9 (1.7 vs. 13.3 min), 0.8 (1.4 vs. 10.1 min) and 0.7 (1.3 vs. 7.6 min) were also seen with sugammadex versus neostigmine [48].

4.2 Reversal of Deep Neuromuscular Blockade

Randomized, safety assessor-blind, multicentre trials examined the efficacy of sugammadex administered at 1–2 PTCs for the reversal of deep neuromuscular blockade [49–53]. The trials included adults who were ASA physical status I–III [49, 52, 53] or I–IV [50, 51] and undergoing surgery [50–52], laparoscopic surgery [49] or outpatient surgery [53] under general anaesthesia induced by propofol and maintained by propofol [49], sevoflurane [50, 51] or inhalational agents [53], with opioids also permitted, or according to local practice [52]. Intravenous sugammadex 4 mg/kg was compared with neostigmine 50 or 70 μg/kg plus glycopyrrolate [50, 51] or atropine [49], with placebo [52], or with spontaneous recovery [53]. Patients receiving sugammadex underwent neuromuscular blockade with rocuronium [49, 50, 52, 53] or vecuronium [51], patients receiving neostigmine underwent neuromuscular blockade with rocuronium [49, 50] or vecuronium [51] and patients recovering spontaneously underwent neuromuscular blockade with rocuronium [52] or succinylcholine [53]. Reversal agents were administered at 1–2 PTCs, except in one trial in which neostigmine was administered at the reappearance of T_2 (i.e. moderate neuromuscular blockade) [49]. The primary endpoint was the time to recovery of the TOF ratio to 0.9 assessed from the start of administration of the reversal agent [49–53], except in patients receiving succinylcholine, in whom the primary endpoint was the time from the start of succinylcholine administration to recovery of the first twitch (T_1) of TOF stimulation to 90 % of baseline [53]. Efficacy was assessed in the modified ITT population [49–52]. One of these studies [53] was a preplanned secondary analysis of a previous trial [54].

Recovery of neuromuscular function from deep neuromuscular blockade was significantly faster with sugammadex than with neostigmine [50, 51] or placebo [52], and recovery from deep neuromuscular blockade with sugammadex was significantly faster than recovery from moderate neuromuscular blockade with neostigmine [49]. The geometric mean time from administration of the reversal agent until recovery of the TOF ratio to 0.9 was significantly shorter with sugammadex than with neostigmine [49–51] or placebo [52] (Table 2). The geometric mean time from administration of the reversal agent until recovery of the TOF ratio to 0.8 or 0.7 was also significantly ($p < 0.0001$) shorter with sugammadex than with neostigmine [50, 51].

Recovery times were less variable with sugammadex than with neostigmine or placebo. In two studies, 94 % [49] and 95 % [52] of sugammadex recipients recovered within 5 min. By contrast, only 20 % of patients receiving neostigmine (which was administered at the reappearance of T_2) recovered within 5 min [49], and ≈30 % of placebo recipients took >2 h to recover [52]. In another study, 70 % of sugammadex recipients recovered within 3 min, whereas it took 30–60 min for 73 % of neostigmine recipients to recover [50]. There was no clinical evidence of residual neuromuscular blockade or recurrence of neuromuscular blockade in sugammadex, neostigmine or placebo recipients [50, 52].

The median times from study drug administration to tracheal extubation or to being ready for operating room (OR) discharge were significantly ($p < 0.0001$) shorter in patients receiving sugammadex than in patients receiving neostigmine, with no significant between-group differences in the median times from OR admission until being ready for OR discharge or from postanaesthesia care unit (PACU) admission to being ready for PACU discharge [49]. The median times from study drug administration to being ready for OR discharge and from OR admission until being ready for OR discharge were significantly ($p < 0.0001$) shorter in patients receiving sugammadex than in patients receiving placebo, with no significant between-group difference in the median time from PACU admission to being ready for PACU discharge [52].

In patients undergoing outpatient surgery, the geometric mean time from administration of the reversal agent until recovery of the TOF ratio to 0.9 was 1.8 min with sugammadex and the geometric mean time from the start of succinylcholine administration to recovery of T_1 to 90 % was 10.8 min [53] (Table 2). The median times from the end of surgery until tracheal extubation, from OR admission to being ready for OR discharge, from OR discharge to being ready for PACU discharge and from PACU admission to being ready for PACU discharge did not significantly differ between the two treatment groups. There was no clinical evidence of residual neuromuscular blockade or recurrence of neuromuscular blockade in either treatment group [53].

Table 2 Efficacy of intravenous sugammadex vs. neostigmine or spontaneous recovery for the reversal of deep neuromuscular blockade or immediate reversal of neuromuscular blockade

Study (study name)	NMBA	Reversal agent	No. of pts	Geometric mean time to recovery of TOF ratio to 0.9[a] (median; range) [min]	Mean time to recovery of T_1[b] (median; range) [min]	
					to 10 %	to 90 %
Reversal of deep neuromuscular blockade at 1–2 PTCs						
Geldner et al. [49]	ROC[c]	SUG 4 mg/kg	66	2.4*[d]		
	ROC[c]	NEO 50 μg/kg[e]	65	8.4[d]		
Jones et al. [50]	ROC[c]	SUG 4 mg/kg	37	2.9*[d] (2.7; 1.2–16.1)		
(SIGNAL)	ROC[c]	NEO 70 μg/kg[e]	37	50.4[d] (49.0; 13.3–145.7)		
Lemmens et al. [51]	VEC[f]	SUG 4 mg/kg	47	4.5*[d] (3.3; 1.4–68.4)		
(SIGNAL)	VEC[f]	NEO 70 μg/kg[e]	36	66.2[d] (49.9; 46.0–312.7)		
Rahe-Meyer et al.	ROC[c]	SUG 4 mg/kg	69	2.2†[d] (2.0; 0.9–20.4)		
[52] (SUNLIGHT)	ROC[c]	PL	65	89.8[d] (95.8; 38.5–289.8)		
Soto et al. [53]	ROC[c]	SUG 4 mg/kg	65	1.8[d] (1.8; 0.5–5.8)		
	SUC[g]	None	77		6.7 (6.7; 1.1–12.8)	10.8[d] (11.3; 2.6–18.3)
Immediate reversal of neuromuscular blockade (3 min post-NMBA)						
Lee et al. [55]	ROC[c]	SUG 16 mg/kg	55		4.4†[d] (4.2; 3.5–7.7)	6.2† (5.7; 4.2–13.6)
	SUC[g]	None	55		7.1[d] (7.1; 3.8–10.5)	10.9 (10.7; 5.0–16.2)

NEO neostigmine, *NMBA* neuromuscular blocking agent, *PL* placebo, *PTC* post-tetanic count, *pts* patients, *ROC* rocuronium, *SUC* succinylcholine, *SUG* sugammadex, *TOF* train of four, T_1 first twitch of TOF stimulation, T_2 second twitch of TOF stimulation, *VEC* vecuronium

* $p < 0.0001$ vs. NEO

† $p < 0.001$ vs. PL or none

[a] Assessed from the start of administration of the reversal agent

[b] Assessed from the start of administration of NMBA. Geometric mean [53] or mean [55] values

[c] Bolus dose of ROC 0.6 mg/kg followed by maintenance with ROC 0.1–0.2 mg/kg [49, 52] or 0.15 mg/kg [50, 53] as needed, or bolus dose of ROC 1.2 mg/kg [55]

[d] Primary endpoint

[e] Glycopyrrolate 14 μg/kg [50, 51] or atropine 10 μg/kg [49] was coadministered with NEO. In one trial, NEO was administered at the reappearance of T_2 [49]

[f] Bolus dose of VEC 0.1 mg/kg followed by maintenance with VEC 0.015 ng/kg as needed

[g] Bolus dose of SUC 1.0 mg/kg

4.3 Immediate Reversal of Neuromuscular Blockade

A randomized, safety assessor-blind, multicentre study examined the efficacy of sugammadex 16 mg/kg in the immediate reversal of neuromuscular blockade ≈3 min after the administration of rocuronium (the maximal pharmacodynamic effect of rocuronium is expected at 3 min) [55]. The trial included adults who were ASA physical status I–II and scheduled to undergo elective surgery under general anaesthesia induced and maintained by propofol or other agents (according to local practice), with opioids also permitted. Neuromuscular blockade was induced by either rocuronium or succinylcholine; sugammadex was administered a mean of 3.1 min (range 2.7–4.2 min) after the start of rocuronium, whereas patients assigned to succinylcholine recovered spontaneously. The primary endpoint was the time from the start of neuromuscular blockade until recovery of T_1 to 10 % of baseline. Efficacy was assessed in the modified ITT population [55].

Recovery from neuromuscular blockade was significantly faster when sugammadex was administered 3 min after rocuronium than when patients were permitted to spontaneously recover from succinylcholine [55]. The mean time to recovery of T_1 to 10 % (4.4 vs. 7.1 min) or 90 % (6.2 vs. 10.9 min) of the baseline value was significantly shorter in patients receiving sugammadex than in those undergoing spontaneous recovery (Table 2) [55].

4.4 Special Patient Populations

Several studies examined the efficacy of sugammadex for the reversal of neuromuscular blockade in various special patient populations, including patients with current or a history of pulmonary disease (e.g. asthma, chronic

Table 3 Efficacy of intravenous sugammadex for the reversal of neuromuscular blockade in special patient populations

Study	Patient cohort	NMBA[a]	Reversal agent	No. of patients	Mean time to recovery of TOF ratio to 0.9[b] (median; range) [min]
Amao et al. [56]	Pulmonary disease	ROC	SUG 2 mg/kg[c]	39	2.1 (2.1; 0.8–12.0)[d]
		ROC	SUG 4 mg/kg[c]	38	1.8 (1.9; 0.7–11.5)[d]
Dahl et al. [57]	Cardiac disease	ROC	SUG 2 mg/kg[c]	38	1.7 (1.7; 0.9–6.9)
		ROC	SUG 4 mg/kg[c]	38	1.4 (1.3; 0.7–3.2)
		ROC	PL	40	34.3 (34.7; 16.9–66.5)
Carron et al. [59]	Morbidly obese	ROC	SUG 4 mg/kg TBW[c]	20	3.1*
		ROC	NEO 70 μg/kg LBW[e]	20	48.6
Fujita et al. [58]	Hepatic dysfunction	ROC	SUG 2 mg/kg[c]	6	2.2 (2.3; 1.4–3.1)[d]
		ROC	SUG 4 mg/kg[c]	10	1.9 (2.0; 1.0–3.3)[d]
	Normal hepatic function	ROC	SUG 2 mg/kg[c]	8	2.0 (1.7; 1.0–3.4)[d]
		ROC	SUG 4 mg/kg[c]	7	1.7 (1.7; 1.4–2.2)[d]
Vymazal et al. [60]	Myasthenia gravis	ROC	SUG 2 or 4 mg/kg[c]	117	2.0 (NR; 1.8–2.1)[d]

IBW ideal bodyweight, *LBW* lean bodyweight, *NEO* neostigmine, *NMBA* neuromuscular blocking agent, *NR* not reported, *PL* placebo, *PTC* post-tetanic count, *ROC* rocuronium, *SUG* sugammadex, *TBW* total bodyweight, *TOF* train of four, T_1 first twitch of TOF stimulation, T_2 second twitch of TOF stimulation

* $p < 0.0001$ vs. NEO

[a] Bolus dose of ROC 0.6 mg/kg [56–58, 60] or 0.9 mg/kg (IBW) [59], followed by maintenance ROC as needed [56–60] (ROC 0.15 mg/kg [56, 59, 60] or 0.1–0.2 mg/kg [57])

[b] Assessed from the start of administration of the reversal agent. Geometric mean [56, 57] or mean [58–60] values

[c] SUG 2 mg/kg administered at the reappearance of T_2 [56–58, 60]. SUG 4 mg/kg administered at the reappearance of T_2 [56, 57], at T_1 if T_2 did not reappear within 15 min of discontinuing ROC [58], if there was no twitch response to TOF stimulation or at the reappearance of T_1 [60] or at 1–2 PTCs [59]

[d] Primary endpoint

[e] NEO plus atropine 10 μg/kg administered at 1–2 PTCs

bronchitis, chronic obstructive pulmonary disease) undergoing noncardiac surgery [56], patients with cardiac disease (i.e. ischaemic heart disease, chronic heart failure, arrhythmia) undergoing noncardiac surgery [57], patients with hepatic dysfunction (liver damage class B or C) undergoing hepatic surgery [58], morbidly obese patients (body mass index $\geq$40 mg/m^2; mean total bodyweight $\approx$130 kg) undergoing laparoscopic removal of gastric banding [59], and patients with myasthenia gravis undergoing surgical thymectomy or cholecystectomy [60]. Comparative trials were of randomized, safety assessor-blind, multicentre design [56, 57], randomized, single-centre design [59] or nonrandomized, single-centre design [58]. Data in patients with myasthenia gravis were obtained from a case series [60]. The trials included adults who were ASA physical status I–III [58, 59], II–III [56] or II–IV [57, 60] and scheduled to receive general anaesthesia induced with propofol [57–60] and maintained with propofol [57, 58], desflurane [59] or isoflurane [60], with opioids also permitted, or according to local practice [56]. Neuromuscular blockade was induced by rocuronium [56–60]. Patients received sugammadex 2 or 4 mg/kg [56–58, 60] or placebo [57] (see Table 3 for further details), with obese patients randomized to receive sugammadex 4 mg/kg (total bodyweight) or neostigmine 70 μg/kg (lean bodyweight) [59]. Primary efficacy endpoints were the time from administration of the reversal agent until recovery of the TOF ratio to 0.9 [56, 58, 60] or the anaesthesia time (i.e. the time from preoxygenation to tracheal extubation) [59]. Efficacy was assessed in the ITT [58, 59] or modified ITT [56, 57] populations.

Sugammadex effectively reversed neuromuscular blockade in various special patient populations. For example, sugammadex 2 or 4 mg/kg was effective in patients with pulmonary disease, with a geometric mean time to recovery of the TOF ratio to 0.9 of 2.1 and 1.8 min (Table 3) [56]. In addition, reversal of neuromuscular blockade was $\approx$20 times faster with sugammadex 2 or 4 mg/kg than with placebo in patients with cardiac disease (Table 3) [57].

The mean time to the recovery of the TOF ratio to 0.9 did not significantly differ between patients with hepatic dysfunction and patients with normal hepatic function who received sugammadex 2 or 4 mg/kg (Table 3) [58].

Reversal of neuromuscular blockade was significantly faster in morbidly obese patients receiving sugammadex 4 mg/kg than in those receiving neostigmine (Table 3), which led to a significantly shorter anaesthesia time with

sugammadex than with neostigmine (48 vs. 95 min; $p < 0.0001$) [59].

Predictable, rapid reversal of neuromuscular blockade was seen with sugammadex 2 or 4 mg/kg in patients with myasthenia gravis [60] (Table 3).

5 Safety and Tolerability of Sugammadex

Intravenous sugammadex was generally well tolerated when administered for the reversal of neuromuscular blockade with rocuronium or vecuronium. A pooled safety analysis reported in the US prescribing information included data from 2914 patients receiving sugammadex 2, 4 or 16 mg/kg and 544 patients receiving placebo in phase I–III studies [6]. Adverse reactions occurring in ≥10 % of sugammadex recipients included pain (48 % of sugammadex 2 mg/kg recipients, 52 % of sugammadex 4 mg/kg recipients and 36 % of sugammadex 16 mg/kg recipients vs. 38 % of placebo recipients), nausea (23, 26 and 23 vs. 23 %), vomiting (11, 12, 15 vs. 10 %), headache (7, 5 and 10 vs. 8 %) and hypotension (4, 5, and 13 vs. 4 %) [6].

Across clinical trials, the most common drug-related adverse events reported in sugammadex and neostigmine recipients included nausea/postprocedural nausea (3–11 vs. 3–18 %) [43, 44, 47, 50, 51], muscle weakness (8 vs. 8 %) [50], dry mouth (0–6 vs. 6–9 %) [43, 47], vomiting (0–5 vs 0–5 %) [43, 44, 47, 50] and procedural complications (0–3 vs. 8–9 %) [47, 50]. The vast majority of drug-related adverse events were of mild to moderate intensity [43, 44, 47, 51], with most studies reporting no serious drug-related adverse events in sugammadex or neostigmine recipients [43, 44, 47, 50, 51].

Significantly ($p < 0.0001$) [43] or numerically [44, 47, 50] higher heart rate and blood pressure values were reported at some time points soon after the administration of neostigmine versus sugammadex in some studies. This may reflect the fact that anticholinergics such as glycopyrrolate (which are coadministered with neostigmine and may be associated with haemodynamic effects such as tachycardia), have a faster onset of action than neostigmine [43].

Anaphylaxis and serious hypersensitivity reactions have been reported in patients receiving sugammadex in clinical trials [6]. In a randomized, double-blind, multicentre study (available as an abstract), healthy adults received three repeat doses of sugammadex 4 mg/kg ($n = 151$), sugammadex 16 mg/kg ($n = 148$) or placebo ($n = 76$), with each dose separated by a washout period of ≈5 weeks [61]. After any dose of study drug, hypersensitivity symptoms (e.g. nausea, pruritus, urticaria) were reported in 6.6 % of sugammadex 4 mg/kg recipients, 9.5 % of sugammadex 16 mg/kg recipients and 1.3 % of placebo recipients [6, 61]. Most hypersensitivity reactions occurred immediately after the administration of sugammadex and were mild and self-limiting. Three subjects who had received sugammadex 16 mg/kg discontinued the study and received treatment with antihistamines and/ or corticosteroids, which led to rapid resolution of hypersensitivity symptoms. Confirmed anaphylaxis occurred in one subject following the first dose of sugammadex 16 mg/kg [61]. Anaphylaxis (characterized by dermatological symptoms such as rash, erythema and urticaria, and hypotension) has also been reported with sugammadex in the postmarketing setting [6], with an estimated rate of adjudicated anaphylaxis alone of 0.008 % and an estimated rate of adjudicated anaphylaxis and hypersensitivity combined of 0.01 % [62]. Sugammadex is contraindicated in patients who have known hypersensitivity to sugammadex or any of its components [6, 25].

Cases of marked bradycardia, including cases which have led to cardiac arrest, have been reported within minutes of administering sugammadex [6, 25]. Most cases of cardiac arrest in the postmarketing setting occurred in patients with serious underlying illnesses or conditions, or in patients experiencing acute processes putting them at significant risk, with no apparent pattern or common element suggesting an association with sugammadex [62]. Patients should be closely monitored during and after reversal of neuromuscular blockade for haemodynamic changes, and anticholinergic agents should be administered in the event of clinically significant bradycardia [6, 25].

Moderate or severe bronchospasm was reported in 2 of 42 patients with underlying asthma who received sugammadex 4 mg/kg [56]. Symptoms of bronchospasm resolved in both patients within 5 min of initiating treatment [56].

6 Dosage and Administration of Sugammadex

Sugammadex is approved in the USA [6] and the EU [25] for the reversal of neuromuscular blockade induced by rocuronium or vecuronium in adults undergoing surgery. Sugammadex is not approved for use in paediatric patients in the USA [6], but is approved for use in paediatric patients aged 2–17 years in the EU [25]. Following rocuronium- or vecuronium-induced neuromuscular blockade, intravenous sugammadex 2 mg/kg is recommended if spontaneous recovery has reached T_2 [6] or up to at least T_2 [25] in response to TOF stimulation and intravenous sugammadex 4 mg/kg is recommended if spontaneous recovery of the twitch response has reached 1–2 PTCs [6] or at least 1–2 PTCs [25]. Intravenous sugammadex 16 mg/kg is recommended if there is a clinical need to reverse neuromuscular blockade soon (≈3 min) after

the administration of a single dose of rocuronium 1.2 mg/kg [6, 25]. Local prescribing information should be consulted for further information concerning contraindications, warnings and precautions pertaining to sugammadex.

7 Place of Sugammadex in Neuromuscular Blockade Reversal

There is a general lack of understanding regarding how best to use NMBAs and reversal agents, and how best to monitor the depth of neuromuscular blockade [63]. Indeed, survey results indicate that NMBAs are often administered without quantitative monitoring of neuromuscular function and that reversal agents are underutilized [63]. ASA guidelines recommend that neuromuscular function should be monitored during emergence and recovery in patients who have received nondepolarizing NMBAs or who have medical conditions associated with neuromuscular dysfunction [64]. Regarding the use of reversal agents, ASA guidelines (which predate the availability of sugammadex and focus on the use of neostigmine and edrophonium), state that specific agents should be administered for reversal of residual neuromuscular blockade when indicated [64].

Reversal agents are usually administered after recovery of the TOF response to T_1 or T_2 (i.e. a moderate level of neuromuscular blockade) [43], with a TOF ratio of $\geq$0.9 considered necessary for full recovery of pharyngeal muscle function and accepted as the target for adequate reversal [44]. Neuromuscular function should be monitored in patients receiving sugammadex until recovery has occurred [65]. In clinical trials, recovery of neuromuscular function from moderate neuromuscular blockade to a TOF ratio of 0.9 was significantly faster and less variable with sugammadex than with neostigmine (Sect. 4.1).

Historically, maintaining deep neuromuscular blockade until the end of surgery has often been avoided, due to the lack of an effective reversal agent [52]. Neostigmine is ineffective in reversing deep neuromuscular blockade and is only used once a degree of spontaneous recovery of neuromuscular function has occurred [51, 53]. Clinical trials demonstrated that sugammadex rapidly reversed deep neuromuscular blockade in a predictable manner (Sect. 4.2). Thus, sugammadex may be particularly useful for reversing deep neuromuscular blockade when surgery ends prematurely or in prolonged surgery when deep neuromuscular blockade is required throughout [50].

Sugammadex was also effective for the immediate reversal of rocuronium-induced neuromuscular blockade (Sect. 4.3), and may be useful when intubation has failed (e.g. in 'cannot intubate, cannot ventilate' situations) [55]. Sugammadex also has potential for use with rocuronium when rapid-sequence induction is required [66–68].

Sugammadex was effective in obese patients (Sect. 4.4). It is recommended that the sugammadex dose be based on actual bodyweight rather than ideal bodyweight or lean body mass (Sect. 3) [6, 25], although this is still a matter of debate. Sugammadex also demonstrated efficacy in other special patient populations, including patients with pulmonary disease, cardiac disease, hepatic dysfunction or myasthenia gravis (Sect. 4.4).

With NMBAs, residual neuromuscular blockade is commonly seen at the end of surgery and may be associated with adverse consequences, including adverse pulmonary outcomes [4, 52]. Residual neuromuscular blockade was not seen when recommended doses of sugammadex and TOF monitoring were used in clinical trials (Sects. 4.1 and 4.2). Sugammadex may also have potential for the rescue of residual neuromuscular blockade if reversal with an AChE inhibitor is incomplete [69, 70], and low-dose sugammadex (i.e. $<$2 mg/kg) successfully reversed shallow, residual, rocuronium-induced neuromuscular blockade [71–73].

Whether the faster recovery from neuromuscular blockade seen with sugammadex versus neostigmine or spontaneous recovery translates into clinical benefits such as improved OR efficiency or a shorter PACU stay is uncertain. In terms of clinical outcomes, mixed results were seen in clinical trials (Sect. 4.2), which were primarily designed to examine the speed of reversal of neuromuscular blockade, rather than health outcome measures. More data concerning the effect of sugammadex on health outcome measures would be of interest, as would pharmacoeconomic analyses examining the cost effectiveness of sugammadex.

The stability of the complex formed by sugammadex and rocuronium or vecuronium means that recurrence of neuromuscular blockade because of dissociation is unlikely. Indeed, recurrence of neuromuscular blockade was not seen in patients receiving sugammadex in clinical trials (Sects. 4.1, 4.2). In addition, the efficacy of sugammadex was not affected by the type of anaesthetic agent (Sect. 2). By contrast, recovery is longer when neostigmine is administered following the use of potent inhalation anaesthetics such as sevoflurane or isoflurane [43, 44, 51]. This may partly explain the slow and variable recovery from neuromuscular blockade seen with neostigmine in some studies [43].

Sugammadex is not metabolized (Sect. 3) and has a low potential for drug interactions (Sect. 2). Sugammadex primarily undergoes renal elimination, meaning that its elimination is delayed in patients with renal impairment (Sect. 3). Sugammadex has been studied in only small numbers of patients with severe renal impairment [29, 74] or end-stage renal disease [75] to date, and is not currently recommended for use in patients with severe renal impairment [6, 25]. High-flux haemodialysis was shown to remove sugammadex and the sugammadex-rocuronium complex [74].

The steroidal NMBA dosage needed to re-establish neuromuscular blockade following administration of sugammadex largely depends on the time elapsed since sugammadex was administered [76]. Local prescribing information should be consulted for recommended waiting times before readministration of rocuronium or vecuronium [6, 25]. A nonsteroidal NMBA should be used if neuromuscular blockade is required before the recommended waiting time has elapsed [6, 25].

The US approval of sugammadex was delayed as the FDA requested additional data, particularly relating to the risk of hypersensitivity reactions [62]. Anaphylaxis and hypersensitivity reactions have been reported in sugammadex recipients, although a clinical trial found that most hypersensitivity reactions occurred immediately following sugammadex administration and were mild and self-limiting (Sect. 5). Prescribing information states that clinicians should be prepared for the possibility of hypersensitivity reactions (including anaphylaxis) and take adequate precautions [6, 25].

Sugammadex had a transient effect on coagulation parameters, although this effect was not considered clinically relevant (Sect. 2). Local prescribing information should be consulted for recommendations pertaining to monitoring of coagulation parameters and other precautions in patients receiving sugammadex [6, 25].

In conclusion, sugammadex is an important option for the rapid reversal of rocuronium- or vecuronium-induced neuromuscular blockade.

Data selection sources:

Relevant medical literature (including published and unpublished data) on sugammadex was identified by searching databases including MEDLINE (from 1946), PubMed (from 1946) and EMBASE (from 1996) [searches last updated 6 June 2016], bibliographies from published literature, clinical trial registries/databases and websites. Additional information was also requested from the company developing the drug.

Search terms: Sugammadex, Bridion, ORG-25969, neuromuscular block*, rocuronium, vecuronium

Study selection: Studies in patients requiring neuromuscular blockade reversal who received sugammadex. When available, large, well designed, comparative trials with appropriate statistical methodology were preferred. Relevant pharmacodynamic and pharmacokinetic data are also included.

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Compliance with Ethical Standards

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