

## Reversal of neuromuscular block

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The use of anticholinesterases to reverse residual neuromuscular block is efficacious only if recovery is already established. It was originally advised that at least the second twitch (T<sub>2</sub>) of the train-of-four response should be detectable before neostigmine is administered. Even in these circumstances, the full effect of anticholinesterases takes up to 10 min to achieve. Anticholinesterases also have muscarinic side-effects that require an antimuscarinic to be administered concomitantly. An ideal reversal agent could be given at any time after the administration of a neuromuscular blocking agent (NMBA), and should have no muscarinic side-effects. The gamma cyclodextrin, sugammadex, has been demonstrated to effectively antagonize even profound block produced by the aminosteroid NMBAs, rocuronium and vecuronium, by chelating them. The complex is then excreted in the urine. Sugammadex is ineffective in antagonizing the benzyliisoquinolinium NMBAs. The dose should be adjusted according to the degree of residual block: sugammadex 16 mg kg<sup>-1</sup> for immediate reversal; 4–8 mg kg<sup>-1</sup> for antagonizing profound block (post-tetanic count 1–2); and 2 mg kg<sup>-1</sup> to antagonize moderate block (when T<sub>2</sub> is detectable). As yet, the extent of any side-effects that may occur with this new antagonist is not fully known, although rarely adverse cardiovascular effects (hypotension, hypertension, prolonged QT interval) have already been reported.

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### History

In the sixteenth century, European explorers encountered natives in the Amazon basin using poison-tipped arrows from the rubber plant *Chondrodendron tomentosum* to kill animals by skeletal muscle paralysis.<sup>82</sup> It was another three centuries before Dale (1914) was to use a derivative of this poison, tubocurarine, to determine that acetylcholine (ACh) was the transmitter at the neuromuscular junction (NMJ).<sup>30</sup> In 1900, Pal,<sup>96</sup> a physiologist in Vienna, had performed experiments on paralysed dogs given curare to study the effects of physostigmine on peristalsis. He observed a marked increase in peristalsis and that the dogs started to breathe spontaneously after its administration. Pal suspected that this drug was acting as an antidote to curare and conducted further experiments to confirm it. In 1912, Læwen<sup>80</sup> demonstrated the clinical usefulness of curarine by injecting it i.m. to achieve abdominal relaxation for peritoneal surgery. But it was not until 1942 that Griffith and Johnson<sup>57</sup> in Montreal introduced curare into clinical anaesthesia. By 1946, the use of neuromuscular blocking agents (NMBAs) had become established in the practice of clinical anaesthesia in Great Britain.<sup>56</sup> Interestingly, in his initial report, Gray<sup>55</sup> only recommended the use of the anticholinesterase, pyridostigmine,

to antagonize residual block 'if clinically indicated'. However, by the mid-1950s, because of repeated reports of incomplete recovery at the end of surgery, neostigmine 5 mg had become an integral part of the 'Liverpool anaesthetic technique'.<sup>8</sup>

### Conventional reversal of neuromuscular block

Cholinesterase inhibitors act indirectly by inactivating the enzyme acetylcholinesterase (AChE) in the synaptic cleft of the NMJ.<sup>9</sup> ACh concentrations increase dramatically, competing with NMBA molecules at the post-synaptic nicotinic receptors.<sup>48</sup> AChE activity gradually returns to normal as the concentration of cholinesterase inhibitor in the plasma and thus at the NMJ decreases as a result of redistribution, metabolism, and excretion. NMBAs are not inactivated or broken down by cholinesterase inhibitors. The cholinesterase inhibitors now most used in clinical practice are neostigmine and edrophonium, which both form a reversible attachment to AChE. Neostigmine forms a covalent bond to

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the esteratic site and edrophonium forms an ionic bond to the anionic site on the AChE molecule. Neostigmine 0.04–0.07  $\mu\text{g kg}^{-1}$  has an onset of action within 1 min but its peak effect does not occur for 9 min,<sup>74</sup> and its duration of action is only 20–30 min.<sup>92</sup> It is metabolized in the liver and approximately 80% of the drug is excreted in the urine within 24 h, 50% of it unchanged.<sup>67 123</sup> These are recognized limitations of the use of anticholinesterase in clinical practice. In addition, it was initially recommended by Ali and colleagues<sup>3</sup> and later by Kirkegaard-Nielsen and colleagues<sup>75</sup> that antagonism of neuromuscular block with an anticholinesterase should not be attempted until two twitches of the train-of-four (TOF) twitch response are detectable, otherwise it will be ineffective.

### Anticholinesterase side-effects

The increase in Ach concentration induced by an anticholinesterase is not limited to the NMJ, but also occurs at muscarinic sites where Ach is the neurotransmitter. Muscarinic side-effects of anticholinesterases include nausea and vomiting, bradycardia and prolongation of the QT interval of the electrocardiograph (ECG),<sup>54</sup> bronchoconstriction,<sup>101</sup> stimulation of salivary glands,<sup>22</sup> miosis, and increased intestinal tone.

### Postoperative nausea and vomiting

Nausea and vomiting are among the most common of postoperative complications, occurring in 30% of patients.<sup>79 120</sup> The effect of neostigmine on the incidence of postoperative nausea and vomiting (PONV) is a controversial issue.<sup>85 95</sup> King and colleagues<sup>73</sup> used neostigmine for reversing neuromuscular block and evaluated the incidence of PONV in 38 patients undergoing elective hip or knee surgery. They found a significant relationship between postoperative emetic symptoms and the administration of neostigmine and atropine. The incidence of nausea in patients receiving neostigmine was 68% compared with 32% ( $P<0.01$ ) in patients in whom no reversal was administered. The incidence of vomiting was 47% with neostigmine compared with 11% ( $P<0.02$ ) in patients who did not receive reversal agent. Joshi and colleagues<sup>72</sup> studied the effects of neostigmine and glycopyrrolate on the incidence of PONV and the need for antiemetics in patients undergoing ambulatory surgery. In contrast, they found that the incidence of PONV and the need for antiemetics did not increase with the use of neostigmine and glycopyrrolate. Similarly, Hovorka and colleagues<sup>65</sup> found that the administration of neostigmine and glycopyrrolate to antagonize neuromuscular block does not increase the incidence or severity of PONV.<sup>65</sup> Evaluating the effect of neostigmine on PONV, Cheng and colleagues<sup>28</sup> extracted data from 933 patients during the early (0–6 h), delayed (6–24 h), and overall postoperative periods (0–24 h). The combination of neostigmine with either atropine or

glycopyrrolate did not significantly increase the overall incidence (0–24 h) of vomiting ( $P=0.48$ ) or nausea ( $P=0.08$ ). There was no significant increase in the risk of vomiting with standard (2.5 mg) compared with smaller (1.5 mg) doses of neostigmine. In contrast to a previous study,<sup>115</sup> they concluded that there is insufficient evidence that neostigmine increases the risk of PONV.

### Q-Tc prolongation

Q-Tc interval prolongation of the ECG occurs with several anaesthetic agents such as sevoflurane,<sup>76</sup> and opioids, and the US Food and Drug Administration (FDA) mandates evaluation of the Q-Tc interval for any new drug undergoing development (ICH 14E).<sup>68</sup> Drug-induced Q-Tc interval prolongation may precipitate life-threatening arrhythmias, is considered a precursor of *torsades de pointes*, and may predict cardiovascular complications.<sup>1 124</sup> Pleym and colleagues<sup>100</sup> described ventricular fibrillation with Q-Tc interval prolongation immediately after reversal with neostigmine; it was considered to be related to the combination of agents used in the case, notably morphine, succinylcholine, thiopental, fentanyl, sevoflurane, neostigmine, and glycopyrrolate, and also other predisposing factors such as a Long QT syndrome, low serum potassium and magnesium, and morbid obesity. There has been another report of a patient with Long QT syndrome who had an episode of cardiac arrest, immediately after neostigmine was given.<sup>107</sup>

### Bronchoconstriction

Cholinergic stimulation produces bronchoconstriction, and anticholinesterases have the potential to increase airway resistance.<sup>40 60</sup> Studying the effect of anticholinergic drugs on rat tracheal slices, Shibata and colleagues<sup>106</sup> found that neostigmine, pyridostigmine, and physostigmine stimulate the phosphatidylinositol response and thus cause bronchoconstriction, while edrophonium has no effect. Co-administration of anticholinergic drugs tend to reduce it.<sup>103</sup> By using neostigmine and atropine to antagonize neuromuscular block in patients with or without chronic obstructive pulmonary disease (COPD), Bourgain and colleagues<sup>20</sup> found that total respiratory resistance was not altered significantly and that changes were similar in COPD and controls. The net effect on airway resistance of the administration of an anticholinesterase with an anticholinergic is unpredictable. These drugs are given at the end of surgery when bronchospasm may be triggered, especially in susceptible patients, by other factors such as the presence of the tracheal tube, pain, and 'light' anaesthesia.

### Postoperative residual paralysis

In order to avoid incomplete reversal of neuromuscular block, monitoring of neuromuscular transmission is

mandatory.<sup>7 77 78</sup> The TOF twitch technique is a clinical tool that can be used both intraoperatively and immediately after surgery, although the latter depends on patient co-operation. Bedside tests such as eye opening, protrusion of the tongue, and maintenance of head lift for 5 s were recommended by Ali and colleagues as alternative signs of adequate recovery. It was shown that the ability to maintain head lift requires a TOF ratio of  $>0.6$ .<sup>3</sup> But it has since been demonstrated that these tests do not ensure adequate muscle strength. Although Ali and colleagues originally suggested that a recovery of the TOF ratio to 0.7 was necessary to protect the airway after tracheal extubation, it is now accepted that a ratio of 0.9 is necessary in this respect.<sup>36 44 46</sup>

Residual paralysis poses a significant risk to patient recovery.<sup>10</sup> The residual presence of volatile anaesthetic agents,<sup>118</sup> benzodiazepines, and narcotics in the tissue compartments contribute to it. Residual paralysis increases the risk of passive regurgitation of gastric contents because of pharyngeal<sup>38</sup> and laryngeal<sup>46</sup> muscle dysfunction, in spite of adequate diaphragm recovery. There is also evidence that non-depolarizing NMBA interfere with hypoxic ventilatory control.<sup>43 45</sup> The hypoxic ventilatory response is reduced by about 30% in awake volunteers when the TOF ratio is only 0.7. The mechanism behind this interaction seems to be a reversible depression of carotid body chemoreceptor activity during hypoxia. This may potentiate postoperative brain injury. Postoperative pulmonary complications,<sup>98</sup> especially atelectasis and pneumonia, are also associated with incomplete reversal.<sup>10</sup> Atelectasis occurs during anaesthesia and is compounded in the postoperative period by any degree of residual paralysis.

### Long-acting NMBAs

Incomplete recovery of neuromuscular function is more common with long-acting non-depolarizing NMBAs,<sup>84 90</sup> but can occur after the use of any of these drugs.<sup>5 15</sup> Spontaneous recovery from neuromuscular block occurs through redistribution, buffered diffusion, and metabolism of the relaxant. Owing to their dependence on organ elimination, the duration of action of long-acting non-depolarizing relaxants is prolonged in the presence of renal,<sup>11 61</sup> hepatic,<sup>2</sup> and cardiac failure. In 1979, Viby-Mogensen and colleagues<sup>119</sup> studied 72 adult patients given *d*-tubocurarine, gallamine, or pancuronium during general anaesthesia. They assessed neuromuscular function in the post-anaesthetic care unit using TOF stimulation. Residual paralysis (TOF ratio  $<0.7$ ) was recorded in 30 patients (42%) and 16 patients (24%) were unable to sustain a head lift for 5 s.

The cause of postoperative residual paralysis is multifactorial.<sup>6</sup> The commonest is the use of inappropriately large doses of NMBA, and too early an attempt to antagonize block. Berg and colleagues<sup>10</sup> recorded the

incidence of residual paralysis (TOF ratio  $<0.7$ ) in 691 patients who received pancuronium, atracurium, or vecuronium intraoperatively. Postoperative paralysis was found to be more common with pancuronium (26%) than atracurium or vecuronium (5.3%). Importantly, the incidence of postoperative pulmonary complications was higher in the elderly, after abdominal or longer lasting surgery ( $>200$  min), and the use of pancuronium (16.9%).

Residual paralysis is also affected by other factors listed in Table 1, including age,<sup>10 39 105</sup> sex, BMI, presence of organ dysfunction, concomitant administration of other drugs, appropriate use of neuromuscular monitoring and reversal agents, and the depth of neuromuscular block at the time of reversal.

### Depth of block

The depth of neuromuscular block at the time of administration of anticholinesterases has an influence on their effect. There is a marked increase in the time to recovery of the TOF ratio to 0.7 if neostigmine is administered at T1  $<10$ – $20\%$  after pancuronium, vecuronium,<sup>12</sup> or rocuronium.<sup>13</sup> Administration of neostigmine to antagonize profound neuromuscular block offers no advantage over waiting for recovery of T2 or spontaneous recovery. Anticholinesterases also exhibit a ceiling effect when used in larger doses.<sup>14</sup> This is not evident with neostigmine  $0.04$ – $0.07 \mu\text{g kg}^{-1}$  but for reversal of profound neuromuscular block, administration of a second dose of neostigmine  $0.07 \mu\text{g kg}^{-1}$  results in no further recovery. In addition, neostigmine 5 mg given after recovery from

**Table 1** Factors contributing to postoperative residual paralysis

Age
Sex (females > males)
Weight
Organ dysfunction
Renal
Hepatic
Cardiac
Neuromuscular
Other drugs
Calcium-channel blockers (e.g. verapamil)
Magnesium
Lithium
Antibiotics (e.g. aminoglycosides)
Local anaesthetics
Volatile agents (e.g. enflurane, sevoflurane)
Opioids
Benzodiazepines
Neuromuscular blocking agent
Choice of agent
Dose, number of increments
Bolus vs infusion
Use of reversal agent
Degree of block at time of administration
Dose
Spontaneous recovery
Acidosis: metabolic or respiratory
Electrolyte imbalance
Hypothermia
Lack of neuromuscular monitoring

vecuronium induced block to a TOF ratio of 0.5, produced recovery to a TOF ratio of 0.7 in 1.1 min compared with only 1.2 min after neostigmine 2.5 mg.<sup>70</sup> It is inappropriate to use an anticholinesterase before at least T2 has been detected: increasing the dose or giving it before this degree of recovery is ineffective.

### *Intermediate-acting NMBAs*

Postoperative residual paralysis has also been reported after the use of intermediate-acting NMBAs such as atracurium,<sup>5 36 47 88</sup> vecuronium,<sup>7 23 47 62</sup> rocuronium,<sup>6 25 36 62</sup> and cisatracurium,<sup>25</sup> and also with the short-acting mivacurium,<sup>27</sup> whether or not a reversal agent has been used.

### *Without reversal*

Baillard and colleagues<sup>7</sup> observed that 42% of patients who received vecuronium but no reversal agent at the end of surgery had evidence of postoperative residual paralysis. Similarly, Hayes and colleagues<sup>62</sup> studying the incidence of postoperative residual paralysis in patients receiving vecuronium, atracurium, or rocuronium but no antagonist, found that 64, 71, and 44%, respectively, had a TOF of <0.8 in the recovery room when not antagonized. van Oldenbeek and colleagues<sup>117</sup> showed that if pancuronium was used during cardiac surgery, 65% of patients remained partially paralysed when they were allowed to emerge from anaesthesia in the ICU. Cammu and colleagues<sup>25</sup> found that patients receiving cisatracurium or rocuronium infusions have a high incidence of postoperative residual curarization when the block was not antagonized. They found that when reversal is not attempted, cisatracurium is safer than rocuronium. Debaene and colleagues<sup>36</sup> also studied the effect of a single dose of vecuronium, rocuronium, or atracurium when not antagonized in 526 patients. On arrival in the post-anaesthesia care unit, the TOF ratio was measured using acceleromyography. Head lift, the tongue depressor test, and manual assessment of TOF and double-burst stimulation fade were performed. TOF ratios <0.7 and 0.9 were observed in 16 and 45% of the patients, respectively. Of the 239 patients tested 2 h later, 10% still had a TOF ratio of <0.7 and 37% had a TOF ratio of <0.9. They concluded that after a single dose of an intermediate-duration NMBA and no reversal, residual paralysis is common, even more than 2 h after its administration.

### *With reversal*

Andersen and colleagues<sup>5</sup> studied 60 patients who received either atracurium 0.6 mg kg<sup>-1</sup> or pancuronium 0.1 mg kg<sup>-1</sup> and an anticholinesterase during anaesthesia. Residual curarization was evaluated clinically and using TOF monitoring. Residual curarization with the use of atracurium was not observed, but it occurred in 30% of patients given pancuronium. Suzuki and colleagues<sup>112</sup> compared the reversal of vecuronium with neostigmine at T1=25% in normal weight, overweight, and obese female

patients. Spontaneous recovery of T1 to 25% was significantly longer in the obese (mean 68.4 min) and the overweight groups (49.3 min) compared with the normal weight group (41.0 min) ( $P<0.05$ ). Recovery after the administration of neostigmine to a TOF ratio of 0.7 did not differ among groups. However, recovery to a TOF ratio of 0.9 in the obese (25.9 min) and the overweight groups (14.6 min) was significantly longer than that in the normal weight group (6.9 min). In a prospective study comparing the incidence of postoperative residual curarization between surgical inpatients and outpatients, Cammu and colleagues<sup>27</sup> found the incidence to be less frequent in surgical outpatients (38%) when compared with inpatients (47%) ( $P=0.001$ ). This may have been the result of more frequent use of mivacurium in the outpatients.

### *Use of neuromuscular monitoring*

Even with intraoperative neuromuscular monitoring, postoperative residual curarization can still occur. Brull and colleagues<sup>23</sup> used TOF stimulation to assess the incidence and degree of residual block in such circumstances in 64 patients in the post-anaesthesia care unit. Within 15 min of admission to the unit, 45% of patients who received pancuronium and 8% who received vecuronium still had a TOF ratio of <0.7.

The ability of conventional peripheral nerve stimulators used intraoperatively to prevent postoperative residual paralysis is unclear. Several studies have suggested that the use of a peripheral nerve stimulator is not associated with a reduced incidence of postoperative residual paralysis. In 2007, Naguib and colleagues<sup>94</sup> conducted a meta-analysis on 24 trials (3375 patients) that were published between 1979 and 2005. They concluded that the incidence of postoperative residual paralysis is significantly lower after intermediate-acting NMBAs, but failed to demonstrate that the use of an intraoperative neuromuscular function monitor decreased the incidence of postoperative residual paralysis.

### *Recurarization*

Recurarization is defined as an increase in neuromuscular block after a variable period of recovery. Recurarization was particularly common with the older NMBAs such as gallamine,<sup>69</sup> *d*-tubocurarine,<sup>104</sup> and pancuronium. The problem was reduced with the advent of atracurium and vecuronium, in part because of other factors such as improved neuromuscular monitoring. It may occur when a long-acting NMBA is antagonized with an anticholinesterase that has a shorter duration of action. Owing to the dynamics of the interaction with the receptor being dependant on the concentration of both the agonist and antagonist, there may be an initial period of recovery from block.<sup>49</sup> As the anticholinesterase is redistributed and metabolized, its concentration falls at the NMJ, but the NMBA is still present. This effect is increased by



respiratory acidosis and inadequate renal function, both of which potentiate the duration of effect of the older agents.

Thus, several techniques may be used to reduce the risk of postoperative residual paralysis, including avoidance of long-acting NMBAs, use of neuromuscular monitoring in the operating theatre, and reversal of block at a TOF count of at least 2. Ideally, any new reversal agent would have a more rapid onset of action, be efficacious irrespective of the degree of neuromuscular block, and have an improved side-effect profile.<sup>66</sup>

## Newer reversal agents

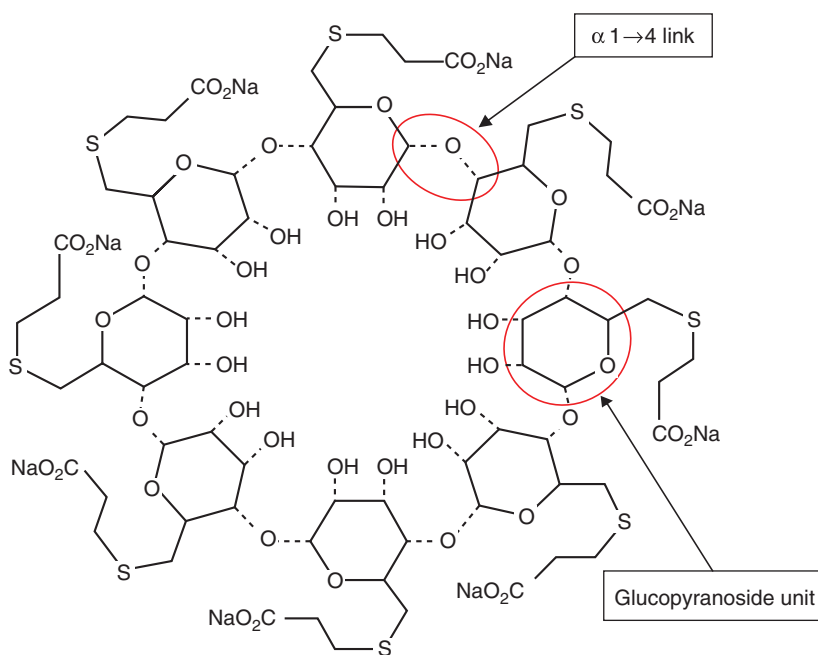
Owing to the limitations of anticholinesterases and the complications of residual neuromuscular block, there has been a quest for an ideal reversal agent. Most of the compounds have been developed with a view to either more effectively suppressing AChE or to indirectly increasing the concentration of ACh.<sup>86</sup> A P<sub>2</sub>-purinoceptor antagonist, suramin, used to treat sleeping sickness, has been shown to antagonize non-depolarizing neuromuscular block, but its short duration of action rendered it inapplicable for clinical use.<sup>63</sup> The potency of oxanilium-based AChE inhibitors such as benzylpiperidinium and benzylpyridinium has been compared with edrophonium and found to be equally potent and free of adverse cardiovascular effects.<sup>59–97</sup> In 2002, Cameron and colleagues<sup>24</sup> synthesized a series of carboxyl-containing cyclophanes as chemical chelators. A few of these compounds were shown by nuclear magnetic resonance imaging to form 1:1 complexes with pancuronium and gallamine but with low

association rate constants (a mathematical constant describing the bonding affinity of two molecules at equilibrium) up to  $10^4 \text{ M}^{-1}$ . Unfortunately, the development of both of these groups of agents, despite showing promise initially, failed to progress as a result of problems with water solubility and potency. Bom and colleagues<sup>17–18</sup> went on to develop one of these concepts by aiming to chelate the newer aminosteroids with compounds of more suitable potency and water solubility. He developed a  $\gamma$ -cyclodextrin, first known as Org 25969. This compound was designed to antagonize rocuronium and had impressive effects in Phase I and II animal studies. It is now available commercially as sugammadex.

## Cyclodextrins

### Structure

Cyclodextrins (sometimes called cycloamyloses), make up a family of cyclic oligosaccharides, composed of  $\alpha$ -D-glucopyranoside units attached by alpha 1 $\rightarrow$ 4 linkages in a circular arrangement (Fig. 1). Natural cyclodextrins are found wherever starch sources, bacteria, and appropriate environmental conditions exist. They contain six to eight glucopyranoside units in a ring, creating a hollow truncated cone known as a doughnut or a *toroid*. Alpha ( $\alpha$ ) cyclodextrins have a six-member sugar ring; beta ( $\beta$ ) cyclodextrins have a seven-member sugar ring, and gamma ( $\gamma$ ) cyclodextrins have an eight-member sugar ring.<sup>113</sup>



**Fig 1** Structure of sugammadex showing eight glucopyranoside units linked together via  $\alpha$  1 $\rightarrow$ 4 linkages to maintain a doughnut-like shape. Reproduced with permission.<sup>121</sup>

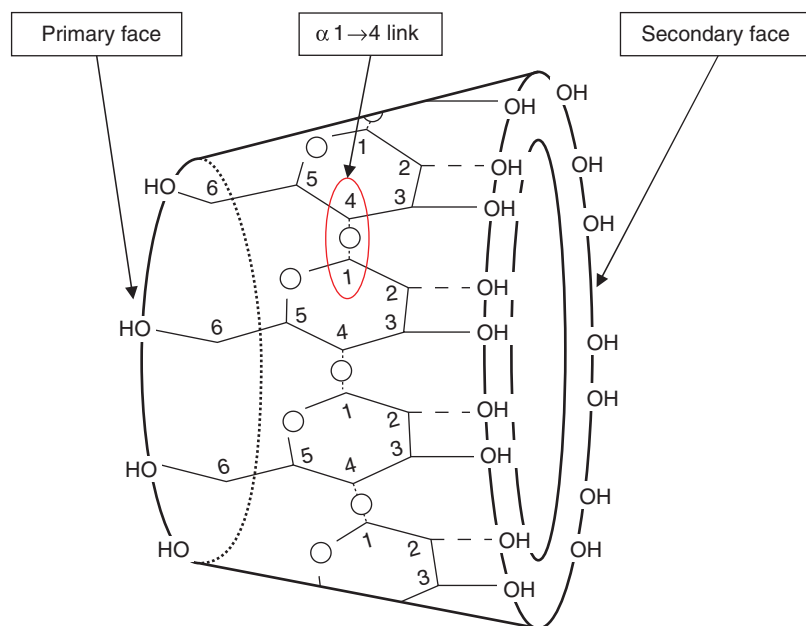
Typically, cyclodextrins have a larger and a narrower opening called the *secondary face* and *primary face*, respectively, which together constitute the toroid (Fig. 2). The negatively charged hydroxyl groups lining the primary and the secondary faces are responsible for the water solubility of these molecules. In contrast, the interior of a cyclodextrin is lined by carbon atoms, which with the alpha 1→4 linkages create a lipophilic cavity. The steric nature of cyclodextrins creates a water soluble molecule capable of surrounding and binding a lipophilic core. Such a structural arrangement is able to encapsulate appropriately sized lipophilic drugs and promote their aqueous solubility.<sup>122</sup> Although cyclodextrins possess both aqueous solubility and an affinity for lipophilic molecules, the relative potency of these characteristics varies between compounds. Close approximation of lipophilic molecules to their corresponding cyclodextrin is necessary to allow non-covalent thermodynamic interactions to occur and promote the formation of an inclusion complex. The approximate cavity sizes of the cyclodextrins are: gamma, 0.8 nm > beta, 0.6 nm > alpha, 0.5 nm. Once inside the cavity, thermodynamic, van der Waals, and hydrophobic interactions, and also hydrogen and charge transfer interactions contribute to the formation of the inclusion complex. An inclusion complex, also known as a host–guest assembly, is the newly formed molecular entity of a cyclodextrin and its encapsulated lipophilic molecule. Szente and colleagues<sup>114</sup> found that substituting atoms or groups on its side units improved the cyclodextrin's activity for a particular molecule. The four steroidal rings of the rocuronium molecule lie in close approximation to the lipophilic cavity of the sugammadex molecule, with the quaternary

ring surrounded by the carboxyl group of the cyclodextrins (Fig. 3).

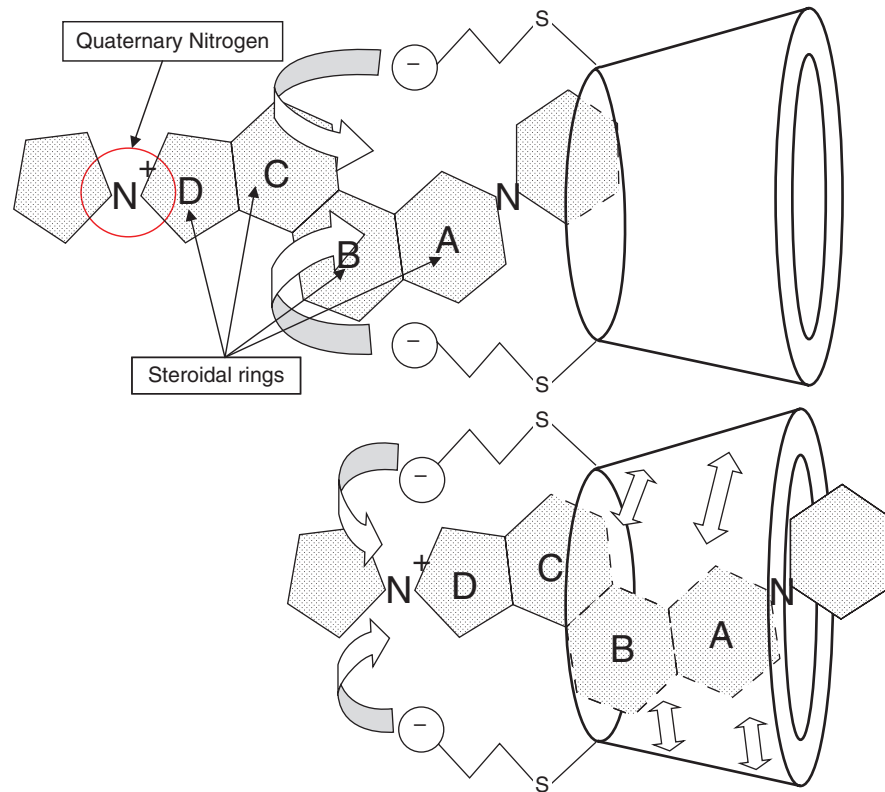
Sugammadex has a molecular weight of 2178 and is highly water soluble. The aqueous solution of sugammadex has a pH of 7.5 and an osmolality between 300 and 500 mOsmol kg<sup>-1</sup>.

### Pharmacokinetics

The volume of distribution of sugammadex is 10–15 litres, similar to extracellular volume, and the plasma elimination half-life ( $t_{1/2}$ ) is 2.2 h. Its clearance is 91 ml min<sup>-1</sup>, which is similar to glomerular filtration rate. It is not metabolized in the body and is excreted unchanged by the kidney, as is the inclusion complex. Sugammadex has low plasma protein binding, minimal blood-brain barrier penetration (<3% in the rat), and minimal placental transfer (<6% in rat and rabbit).<sup>51</sup> Sugammadex and rocuronium both have three-compartment kinetics that can be explained by a dynamic interaction model. This model assumes that the pharmacokinetics of the sugammadex/rocuronium complex is similar to that of sugammadex alone and that complex formation takes place in the central compartment only. In contrast to earlier compounds, the sugammadex/rocuronium complex has a very high association rate of 10<sup>7</sup> M<sup>-1</sup> as determined by isothermal titration calorimetry, and a very low dissociation rate. It is estimated that, for every 25 million sugammadex/rocuronium complexes that are formed, only one complex dissociates.<sup>18</sup> Sugammadex has no intrinsic pharmacological activity, and it exhibits no reproductive toxicity, teratogenicity, or genotoxicity in animals.



**Fig 2** Structural arrangements of glucopyranose units in a  $\gamma$ -cyclodextrin, showing negatively charged hydroxyl groups at the rims creating the *primary* and *secondary* faces. Reproduced with permission.<sup>121</sup>



**Fig 3** The encapsulation process: sugammadex carboxyl groups interact with the steroidal rings A, B, C, and D of the aminosteroid NMBA molecule drawing it into the cavity of the cyclodextrin where additional non-covalent attractions ( $\leftrightarrow$ ) hold the molecule securely in place. Reproduced with permission.<sup>122</sup>

### Mechanism of action

Sugammadex forms a 1:1 inclusion complex with steroidal non-depolarizing NMBAs (rocuronium > vecuronium >> pancuronium), thereby terminating their action. After i.v. administration, sugammadex binds to free rocuronium molecules in the plasma, decreasing their free concentration. This creates a concentration gradient, promoting the movement of rocuronium away from the NMJ back into the plasma where it is further encapsulated by sugammadex molecules. Neuromuscular block is rapidly terminated. However, the total concentration of rocuronium (free and bound) is increased in the plasma.<sup>42–53</sup> Unlike anticholinesterase drugs, sugammadex has no effect on AChE. This obviates the need for anticholinergic drugs, thus avoiding their side-effects.

### Drug interactions

The interaction of sugammadex with other molecules has also been tested using isothermal titration microcalorimetry. This technique measures the heat production when two molecules form a complex. The ability of sugammadex to form complexes with other steroidal and non-steroidal compounds such as cortisone, atropine, hormonal contraceptives, remifentanyl, verapamil, fusidic acid, and flucloxacillin is insignificant and approximately

120–700 times less than that of rocuronium.<sup>125</sup> However, it is recommended that flucloxacillin 500 mg or more should be avoided for 6 h after sugammadex and missed dose advice followed in patients taking progesterone oral contraceptives who are given sugammadex.<sup>21</sup> The endogenous steroids and other steroidal drugs lack the charged quaternary nitrogen on the ammonium group of NMBAs that binds to the negatively charged carboxyethyl side chains of sugammadex (Fig. 3). Furthermore, steroidal hormones are tightly bound to specific protein carriers (e.g. sex hormones are bound with very high affinity to globulin), reducing their accessibility to sugammadex.

Sugammadex is ineffective against depolarizing NMBAs (succinylcholine) and benzyliisoquinoliums (atracurium and mivacurium),<sup>32</sup> as it cannot form a host–guest complex with them. Clinically, this is relevant if neuromuscular block has to be re-established after reversal with sugammadex. Cisatracurium causes more intense block in anaesthetized guinea pigs with a faster onset when administered after sugammadex has been used to reverse rocuronium.<sup>19</sup> Succinylcholine also produced complete block in the same model, although the onset was delayed.<sup>19</sup> It is recommended that benzyliisoquinolium NMBAs are used if paralysis is necessary after reversal with sugammadex. However, rocuronium will still have an effect, although

less profound in such circumstances (a maximum of 79% of control).<sup>34</sup>

### Animal studies

Using single twitch stimulation, de Boer and colleagues<sup>33</sup> evaluated the capacity of nine synthetic cyclodextrins (Org 25288, Org 25289, Org 25467, Org 25168, Org 25169, Org 25555, Org 25166, Org 26142, and Org 25969) to antagonize a constant neuromuscular block induced by infusion of rocuronium in the rhesus monkey and compared it with reversal by neostigmine and atropine. The results showed a more rapid recovery of block with Org 25969 and Org 26142 when compared with the anticholinesterase ( $P < 0.05$ ). No signs of residual block or change in blood pressure or heart rate were observed. Animal studies subsequently demonstrated the effectiveness of Org 25969 as a reliable reversal agent of steroidal NMBAs in mouse hemidiaphragm,<sup>91</sup> guinea pigs,<sup>42</sup> monkeys,<sup>32</sup> and cats.<sup>64</sup>

Miller and colleagues<sup>91</sup> antagonized neuromuscular block in the mouse hemidiaphragm with the phrenic nerve intact. A 90% block was achieved using different NMBAs. After confirmation of paralysis, increasing doses of sugammadex were administered. The return of muscle contraction was measured. They found that rocuronium was most easily antagonized followed by rapacurium, vecuronium, and pancuronium. The depolarizing agent succinylcholine and the benzylisoquinolone NMBAs, atracurium and mivacurium, were not antagonized. Mason and colleagues<sup>87</sup> studied the recovery characteristics after a bolus and infusion of rocuronium in anaesthetized guinea pigs. After achieving 90% neuromuscular block, the infusion was stopped and sugammadex 1 mg kg<sup>-1</sup> was administered. Recovery from block to a TOF ratio of  $\geq 0.9$  occurred after all the aminosteroid NMBAs in  $< 1$  min. The time to recovery from non-steroidal NMBAs was not significantly better than spontaneous recovery.<sup>87</sup>

van Egmond and colleagues<sup>116</sup> used rocuronium and vecuronium to achieve 90% block in anaesthetized rhesus monkeys followed by sugammadex 1.0 mg kg<sup>-1</sup>. The spontaneous time to recovery of the TOF ratio to 0.5, 0.7, and 0.9 was also noted. Recovery to a TOF ratio of 0.9 after sugammadex 1.0 mg kg<sup>-1</sup> was achieved in 1.9 and 4.4 min in the rocuronium and vecuronium groups, when compared with spontaneous recovery of 14.5 and 23.1 min, respectively ( $P = 0.05$ ).<sup>116</sup>

Epemolu and colleagues<sup>42</sup> determined the changes in plasma concentration of rocuronium and its reversal after an infusion of Org 25969 in anaesthetized guinea pigs. They achieved a steady-state 90% block by infusing rocuronium 12–19 nmol kg<sup>-1</sup> min<sup>-1</sup>. After a 30 min infusion, they compared the plasma concentration of rocuronium when Org 25969 or normal saline was infused. They found that the plasma concentration of rocuronium remained at steady state in the saline group, but in the Org 25969 group an increase in the total plasma concentration

of rocuronium (free and complexed) was observed even though the rate of rocuronium infusion was unchanged. They concluded that the capture of rocuronium by Org 25969 caused a fall in its free plasma concentration, encouraging transfer of rocuronium from the effect compartment to the central compartment where it is further bound to Org 25969.

### Human studies

#### Phase I trials

In 2005, Gijsenbergh and colleagues<sup>53</sup> studied the safety, efficacy, and pharmacokinetics of sugammadex for the first time in 29 healthy male volunteers. This double-blind trial was divided into two parts. In Part I, 19 conscious volunteers received either sugammadex or placebo. Plasma and urinary concentrations of sugammadex were measured over 480 min. In Part II, another 10 volunteers received general anaesthesia and rocuronium 0.6 mg kg<sup>-1</sup>. Sugammadex or placebo was given, 3 min after rocuronium. Six doses of sugammadex ranging from 0.1 to 8.0 mg kg<sup>-1</sup> were evaluated. Inadequate recovery from neuromuscular block was seen in doses of sugammadex  $< 1.0$  mg kg<sup>-1</sup>, and its effect reached a plateau at doses of 4.0–8.0 mg kg<sup>-1</sup>. Importantly, subjects receiving sugammadex 8.0 mg kg<sup>-1</sup> recovered from profound neuromuscular block to a TOF ratio of 0.9 in 1 min compared with 52 min with placebo, suggesting that this new drug could have a role in the ‘cannot intubate, cannot ventilate’ situation, a scenario where anticholinesterases have no effect. There was no evidence of recurarization in the 90 min after sugammadex administration. All adverse events related to sugammadex were of limited duration and intensity, except for a period of paraesthesia in the injection arm in one volunteer receiving sugammadex 8 mg kg<sup>-1</sup>. The study noted eight episodes of QT interval prolongation in six subjects, of which five occurred in the placebo group.

Concerned about the prolongation of QT interval reported in previous studies, Cammu and colleagues<sup>26</sup> evaluated the effect of higher doses of sugammadex combined with a single dose of rocuronium or vecuronium in 16 healthy volunteers.<sup>26</sup> To eliminate the effect of potent inhalation agents on QT interval, they anaesthetized the subjects with a propofol/remifentanyl infusion. Twelve subjects received sugammadex 16, 20, or 32 mg kg<sup>-1</sup> combined with either rocuronium 1.2 mg kg<sup>-1</sup> or vecuronium 0.1 mg kg<sup>-1</sup>. Four subjects were not anaesthetized and received the same doses. Plasma concentrations of sugammadex, rocuronium, and vecuronium were measured. The ECG and vital signs showed no clinically relevant changes.

In a double-blind, cross-over study, de Kam and colleagues<sup>35</sup> allocated 62 volunteers randomly to receive single doses of sugammadex 4.0 mg kg<sup>-1</sup> (therapeutic



**Table 2** Q-Tc interval prolongation after sugammadex 4.0, 32.0, and moxifloxacin 400 mg in healthy volunteers<sup>35</sup>

	Sugammadex		Moxifloxacin 400 mg
	4.0 mg kg <sup>-1</sup>	32.0 mg kg <sup>-1</sup>	
Largest time-matched mean Q-Tc interval difference to placebo (ms)	1.8	2.8	18.6
One-sided 95% upper confidence limit (ms)	4.3	5.3	21.8

dose), sugammadex 32.0 mg kg<sup>-1</sup> (supra-therapeutic dose), moxifloxacin 400 mg (a positive control that has a Q-Tc interval prolonging effect in healthy volunteers), or placebo. According to the ICH-E14,<sup>68</sup> a thorough Q-Tc study is negative if assay sensitivity is demonstrated by moxifloxacin showing Q-Tc interval prolongations more than 10 ms longer than placebo. Additionally, the 95% upper confidence limit for the largest time-matched mean Q-Tc difference compared with placebo should be a <10 ms margin. Table 2 demonstrates that the Q-Tc prolongations for sugammadex 4.0 and 32.0 mg kg<sup>-1</sup> are well below 10 ms.

### Phase II trials

As demonstrating the safety and efficacy of sugammadex in Phase I studies, several dose-finding Phase II studies have been conducted into the ability of sugammadex to antagonize any degree of neuromuscular block produced by either rocuronium or vecuronium (not pancuronium).

### Moderate block

Shields and colleagues<sup>108</sup> administered sugammadex 0.5–6.0 mg kg<sup>-1</sup> to patients given rocuronium [0.6 mg kg<sup>-1</sup> followed by repeated increments to maintain profound block at a post-tetanic count (PTC) of <10 for at least 2 h]. After recovery to T2, sugammadex antagonized block in a dose-dependant fashion with recovery times of <2 min when >1.0 mg kg<sup>-1</sup> was used. There was no evidence of recurarization.

Suy and colleagues<sup>111</sup> evaluated the efficacy of sugammadex 0.5 and 4.0 mg kg<sup>-1</sup> to reverse moderate neuromuscular block (reappearance of T2) induced by rocuronium and vecuronium in 80 patients. The mean time for recovery of the TOF ratio to 0.9 in the rocuronium group was 31.8 min after placebo compared with 3.7 and 1.1 min after sugammadex 0.5 and 4.0 mg kg<sup>-1</sup>, respectively. The mean times in the vecuronium group were 48.8 min after placebo, compared with 2.5 and 1.4 min after sugammadex 1.0 and 8.0 mg kg<sup>-1</sup>, respectively.

### Profound block

Pühringer and colleagues<sup>102</sup> studied recovery from a high-dose rocuronium (1.0–1.2 mg kg<sup>-1</sup>) using sugammadex 2–16 mg kg<sup>-1</sup> compared with placebo. Sugammadex 16

mg kg<sup>-1</sup> administered 3 or 15 min after rocuronium 1.0 mg kg<sup>-1</sup> decreased the median recovery of the TOF to 0.9 from 111.1 and 91.0 min in the placebo groups to 1.6 and 0.9 min, respectively, after sugammadex. After rocuronium 1.2 mg kg<sup>-1</sup>, sugammadex 16 mg kg<sup>-1</sup> decreased the time from 124.3 min (3 min group) and 94.2 min (15 min group) in the placebo groups to 1.3 and 1.9 min, respectively. Exploratory ECG analysis revealed that prolongation of the corrected QT interval, possibly related to sugammadex, occurred in one patient. Another two patients developed markedly high arterial pressure after sugammadex that lasted approximately 15 min.

de Boer *et al.*<sup>31</sup> antagonized rocuronium 1.2 mg kg<sup>-1</sup> with sugammadex 2–16 mg kg<sup>-1</sup> administered 5 min later. Increasing doses of sugammadex reduced the mean recovery time from 122 min (spontaneous) to <2 min. Groudine and colleagues<sup>58</sup> enrolled 50 patients to study the efficacy of sugammadex in reversing profound block (PTC 1–2). Subjects anaesthetized with nitrous oxide and propofol received either rocuronium 0.6 or 1.2 mg kg<sup>-1</sup> and one of five doses of sugammadex. Reversal of neuromuscular block was obtained after administration of sugammadex in all but the lowest doses (0.5–1.0 mg kg<sup>-1</sup>). At the 2 mg kg<sup>-1</sup> dose, all patients were antagonized with sugammadex, but there was significant variability in recovery of the TOF ratio to 0.9 (1.8–15.2 min). Variability decreased and speed of recovery increased in a dose-dependent manner. At the highest dose (8 mg kg<sup>-1</sup>), mean recovery time was 1.2 min (range 0.8–2.1 min).

These Phase II studies have shown that sugammadex is capable of reversing profound block induced by rocuronium or vecuronium in a dose-dependant manner, which cannot be replicated with the anticholinesterases. In addition, a small study of 20 patients has demonstrated satisfactory reversal from pancuronium-induced block at reappearance of T2 with sugammadex 2.0–8.0 mg kg<sup>-1</sup>.<sup>37</sup>

### Phase III trials

These are carried out after dose-finding studies have been performed to obtain further data on a drug's safety and efficacy.

### Moderate block

Phase III trials have demonstrated the efficacy of sugammadex compared with neostigmine given with glycopyrrolate or atropine in antagonizing block produced by aminosteroidal NMBAs. In a randomized trial, 198 patients received sugammadex or neostigmine administered at reappearance of T2.<sup>16</sup> Significantly faster recovery to a TOF ratio of 0.9 occurred after sugammadex. Median time (range) to recovery was 1.4 (0.9–5.4) min for sugammadex vs 17.6 (3.7–106.9) min ( $P<0.0001$ ) for neostigmine after rocuronium; and 2.1 (1.2–64.2) min vs 18.9 (2.9–76.2) min ( $P<0.0001$ ), respectively, after vecuronium.

Comparing sugammadex for the reversal of rocuronium-induced block with that of neostigmine–glycopyrrolate for cisatracurium-induced block, Flockton and colleagues<sup>50</sup> studied 84 patients who received either rocuronium 0.6 mg kg<sup>-1</sup>/sugammadex 2 mg kg<sup>-1</sup> or cisatracurium 0.15 mg kg<sup>-1</sup>/neostigmine 50 µg kg<sup>-1</sup>. Reversal agents were administered after the reappearance of T<sub>2</sub> detected using acceleromyography. They found that the time to recovery of the TOF ratio to 0.9 was faster with sugammadex (2.0 min) than with neostigmine (8.8 min) ( $P<0.0001$ ).

### Profound block

Jones and colleagues<sup>71</sup> compared sugammadex with neostigmine/glycopyrrolate for the reversal of profound rocuronium-induced neuromuscular block. Seventy-four patients anaesthetized with propofol, sevoflurane, and an opioid, received rocuronium 0.6 mg kg<sup>-1</sup> with maintenance doses of 0.15 mg kg<sup>-1</sup> as required to maintain profound block (PTC 1–2). They were then randomly administered sugammadex 4 mg kg<sup>-1</sup> or neostigmine 70 µg kg<sup>-1</sup> and glycopyrrolate 14 µg kg<sup>-1</sup>. The mean time to return of the TOF to 0.9 with sugammadex was 2.9 min vs 50.4 min with neostigmine–glycopyrrolate ( $P<0.0001$ ). Ninety-seven per cent of patients who received sugammadex recovered to a TOF ratio of 0.9 within 5 min. In contrast, most of the patients who received neostigmine (73%) only recovered between 30 and 60 min after administration, with 23% requiring >60 min to recover to a TOF ratio of 0.9 during sevoflurane anaesthesia. The effect of the potent inhalation agent was probably of significance in this respect. Sugammadex will be of use in antagonizing profound rocuronium block where it is recognized that neostigmine will be ineffective.

Lemmens and colleagues<sup>83</sup> compared sugammadex with neostigmine/glycopyrrolate for the reversal of profound vecuronium-induced neuromuscular block (PTC 1–2). They found that the mean time to recovery of the TOF ratio to 0.9 was significantly faster with sugammadex compared with neostigmine (4.5 vs 66.2 min,  $P<0.0001$ ). They concluded that recovery from neuromuscular block induced by vecuronium was 15 times faster with sugammadex 4 mg kg<sup>-1</sup> compared with neostigmine 70 µg kg<sup>-1</sup> when given at a PTC of 1–2.

### Immediate reversal

Lee and colleagues<sup>81</sup> enrolled 110 patients to compare the use of sugammadex for the immediate reversal of rocuronium-induced block with that of spontaneous recovery from succinylcholine. Anaesthesia was induced and maintained with propofol and opioid given as clinically indicated. The patients received either rocuronium 1.2 mg kg<sup>-1</sup> followed 3 min later by sugammadex 16 mg kg<sup>-1</sup>, or succinylcholine 1.0 mg kg<sup>-1</sup> with spontaneous recovery. From the start of NMBA administration, mean (SD) time to

recovery of T1 to 90% was faster in the rocuronium/sugammadex group 6.2 (1.8) min when compared with succinylcholine, 10.9 (2.4) min ( $P<0.0001$ ). They concluded that faster recovery from rocuronium-induced profound block compared with spontaneous recovery from succinylcholine may be useful for immediate reversal in a 'cannot intubate, cannot ventilate' situation.

### Special populations

Phase III trials have been carried out to study sugammadex in the elderly and paediatric populations and in patients with renal, cardiac, and pulmonary disease. McDonagh and colleagues<sup>89</sup> evaluated sugammadex for reversal of moderate rocuronium-induced neuromuscular block in younger compared with older adults. This trial included 48 patients aged 18–64 yr in the younger group, 62 older patients (65–74 yr), and 40 in a very elderly age group (≥75 yr). Neuromuscular block was antagonized on reappearance of T2 with sugammadex 2 mg kg<sup>-1</sup> after facilitating tracheal intubation with rocuronium 0.6 mg kg<sup>-1</sup> followed by increments of 0.15 mg kg<sup>-1</sup> as required. The mean time from administration of sugammadex to recovery of the TOF ratio to 0.9 was 2.3 min in the younger and 3.6 min in the very elderly group. The mean recovery time of the TOF ratio to 0.9 was only 36 s faster in the younger adults compared with the other groups combined (2.9 min), but it was a statistically significant difference ( $P=0.022$ ). This could be because of a lower cardiac output in the older patients.

Plaud and colleagues<sup>99</sup> studied sugammadex, given at reappearance of T2, for the reversal of rocuronium-induced block in paediatric and adult patients. Patients were stratified into four groups: infants (28 days to 23 months), children (2–11 yr), adolescents (12–17 yr), or adults (18–65 yr). Anaesthesia was maintained with i.v. propofol and an opioid. At the reappearance of T2, a single dose of sugammadex (0.5, 1.0, 2.0, or 4.0 mg kg<sup>-1</sup>) or placebo was administered. The median time to recovery of the TOF ratio to 0.9 with sugammadex 2.0 mg kg<sup>-1</sup> was 1.2 min in children and 1.1 min in adolescents, but the numbers in each group were small. Additional studies will be required to fully determine the efficacy and safety of sugammadex in infants and children.

Dahl and colleagues<sup>29</sup> studied the effect of sugammadex in patients with cardiac disease (ischaemic heart disease, chronic heart failure, or arrhythmia). One hundred and twenty-one patients undergoing elective non-cardiac surgery were included. The primary objective was to evaluate the safety of sugammadex 2 and 4 mg kg<sup>-1</sup> compared with placebo in cardiac patients. No patient was given neostigmine in this study. QTc (F) was measured using a formula based on the Fridericia (primary) model for calculating the QT duration of the ECG according to the frequency of the heart beat.<sup>52</sup> The time to recovery to a TOF ratio of 0.9 after reversal at reappearance of T2 was

1.7 min with sugammadex 2 mg kg<sup>-1</sup> and 1.4 min with 4 mg kg<sup>-1</sup> compared with placebo (34.3 min). The study showed no significant prolongation of the Q-Tc (F) interval, but the authors reported three patients, one in each treatment group, of slight prolongation of the Q-Tc (F) interval. This could have been related to the use of either propofol or an opioid during total i.v. anaesthesia. They concluded that sugammadex can be administered safely to patients with cardiac disease undergoing non-cardiac surgery.

To study the effect of sugammadex in patients with pulmonary disease, Amao and colleagues<sup>4</sup> enrolled 86 ASA II–III patients with a diagnosis or history of pulmonary disease. They reported two incidences of bronchospasm, both in the sugammadex 4 mg kg<sup>-1</sup> group and both in patients with a history of asthma. These episodes lasted <5 min and resolved with salbutamol/terbutaline administration. Both were classed as serious adverse effects. No recurarization was observed in any patient. They concluded that the absence of cholinergic activity with sugammadex makes it an appropriate agent for reversal of neuromuscular block in patients with pulmonary complications.

A small study has been reported of the use of sugammadex to antagonize moderate block produced by rocuronium in patients with renal failure.<sup>110</sup> There was no significant difference in the effect of sugammadex 2.0 mg kg<sup>-1</sup> on the recovery from block in this group compared with healthy controls. As sugammadex is excreted entirely in the urine, a study of its pharmacokinetics in this population is awaited.

### Adverse events

The clinical trial data on the use of sugammadex in more than 2000 patients has demonstrated that it is well tolerated. The safety profile is comparable with that of other cyclodextrins used as carrier agents (e.g. for i.v. itraconazole and alprostadil).<sup>51</sup> Common adverse effects reported after its use include procedural pain, nausea, vomiting, pyrexia, headache, sore throat, back pain, cough, and constipation. It is likely that some of these side-effects are because of other agents administered during the anaesthetic.

Interestingly, however, in at least two of the sugammadex studies, urinalysis tests have demonstrated transient increases in urinary creatinine,  $\beta_2$ -microglobulin, microalbumin, or *N*-acetyl- $\beta$ -glucosaminidase (NAG) after its use, the cause of which is unknown.<sup>50 109</sup> The cells of the proximal tubular epithelium of the nephron, being of high metabolic activity, are very susceptible to hypoxia. NAG is an enzyme found in these cells and an increase in its urinary concentration is considered to be an indirect marker of ischaemic tubular damage. In the Flockton study, urinary NAG concentrations were increased in 16 patients given sugammadex and 14 patients in the neostigmine group, but returned to normal values within 24 h.<sup>50</sup>

No long-term sequelae were reported, and the significance of these findings is unknown.

Along with the Q-Tc changes and the hypertension, it should be noted that episodes of hypotension have also been reported after sugammadex 2–4 mg kg<sup>-1</sup>.<sup>109</sup> In contrast, one report described an inadvertent overdose of sugammadex (40 mg kg<sup>-1</sup>) without ill effect on the cardiovascular system.<sup>93</sup>

There have been six reports in volunteer studies of possible allergic reactions to sugammadex, one of which has been substantiated by a positive skin test.<sup>51</sup> This is of particular interest as it is one of the reasons for the delay in approval of sugammadex by the FDA in the United States. Further volunteer studies are continuing in this respect. Some transient deterioration in recovery from block has also been reported when only a small dose of sugammadex was used. Eleveld and colleagues<sup>41</sup> noted a temporary decrease in the height of T1 and the TOF ratio after reversal of rocuronium 0.9 mg kg<sup>-1</sup> with sugammadex 0.5 mg kg<sup>-1</sup>, administered 42 min later at a PTC of only 1.<sup>41</sup> The TOF ratio subsequently recovered to 0.9, 60 min later, with no adverse effect.

### Conclusions

Although the use of anticholinesterases, such as neostigmine, to reverse residual neuromuscular block is ubiquitous, these drugs do have limitations. They have muscarinic side-effects and to be effective, they should not be administered until recovery from block has been established.

The advent of the  $\gamma$ -cyclodextrin, sugammadex, which will reliably reverse even profound block produced by aminosteroid NMBAs will be advantageous especially in a 'cannot intubate, cannot ventilate' scenario. It is too soon to know the extent of any side-effects produced by this drug. At present, its limitations seem to be confined to its cost, and its inability to reverse non-aminosteroidal agents.

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