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BRIDION Sugammadex, Progress in Anaesthesiology

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Abstract

Neuromuscular blocking agents are the substantial element of anesthesia in almost every surgical field. Nevertheless their use may be associated with rise in morbidity and mortality. Of importance are: the general state of the patient, liver and renal function, muscle relaxants metabolism, excretion, side effects and, above all, residual neuromuscular blockade. Prophylaxis of insufficient block reversal consists of proper dosing and timing of the muscle relaxant, neuromuscular transmission monitoring and pharmacologic reversal of the blockade. An ideal antagonistic agent reverses muscle paralysis rapidly and completely, disregarding its depth and total dose of muscle relaxant, has no side effects and is excreted by kidneys. The criteria are met by cyclodextrin gamma — sugammadex. In contrast to anticholinergic agents, which enhance the acetylcholine amount in the postsynaptic part of the neuromuscular junction, sugammadex encapsulates myorelaxant agent removing it from the junction.

Being authorized in 2008 sugammadex – Bridion is well known in Europe, but still used mostly in specific situations: CNI CNV, unexpectedly short time of surgical intervention, extreme obesity, neurologic pathology.

Keywords: Acceleromyography, Bridion, Neuro-Muscular Blockade, Residual Block, Sugammadex, TOF.

Jurgen Thorwald, in his book "**The Century of the Surgeon**" highlights the profound impact of anaesthesia on the development of surgery. He emphasizes that the elimination of pain through anaesthesia paved the way for surgical advancements, allowing for more complex and prolonged procedures. Thorwald acknowledges anaesthesia as a "divine deed" in alleviating human suffering (Thorvald, 1956).

According to John S. Lundy general anaesthesia is well balanced on three elements:

Sleep - lack of consciousness,
Analgesia - lack of pain and autonomic reflexes,
Muscle relaxation - lack of skeletal muscle movements (Lundy & Saunders, 1946).

Proper neuromuscular blockade enables quick, nontraumatic tracheal intubation, well controlled skeletal muscle paralysis during surgical procedure, quick reversal of blockade with no side effects and no residual block. Muscle relaxants permit surgical conditions to be achieved with lesser doses and lower concentration of anaesthetic drugs (Lebowitz & Ramsey, 1987).

Table 1

Recommendation for Neuro - Muscular Blockade Reversal
Use muscle relaxants of short or intermediate time of action
Avoid muscle relaxants with active metabolites
Monitor the neuromuscular block depth
Maintain the level of blockade during anaesthesia
Aim to have three or four twitches visible at the time of relaxant reversal
Adjust the dose of reversing agents according to the depth of block
Assess recovery by clinical criteria and TOF before discontinuing ventilatory support
Monitor TOF during recovery

The most common question is: „should neuromuscular blockade be reversed?" Spontaneous reversal after single intubation dose of a nondepolarizing muscle relaxant occur within 50 - 150 min. But residual blockade can be detected even after 4-7 hours after pharmacologic reversal /Fig 1/.

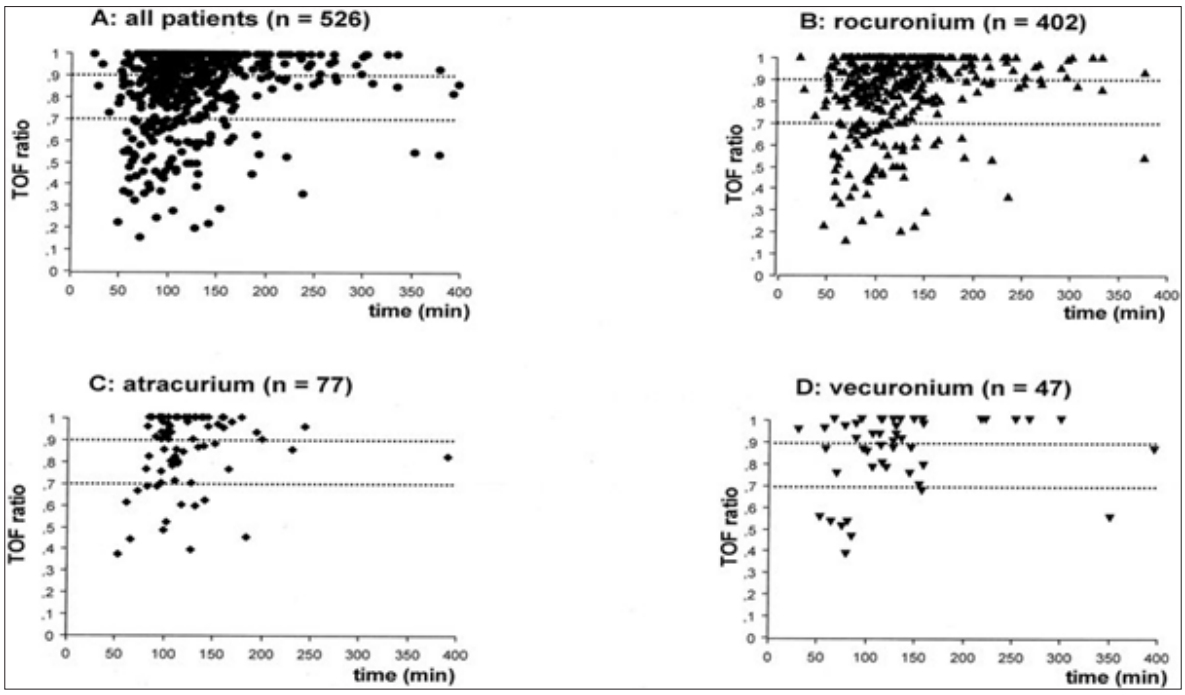


Figure 1: Residual blockade was reported in 5-10 %, even when pharmacologic reversal is a standard and in 33-45 % of patients in whom reversal was not ordered (Booij & Drobnik, 2009).

Residual block has no influence on central respiratory drive; the breathing is efficient, tidal volume TV maintained as long as the diaphragm movements are efficient. Unfortunately diaphragm is the muscle most affected by residual blockade, The other muscles also susceptible are pharyngeal and laryngeal muscles / *m. constrictor pharyngis superior and inferior, m. cricothyroideus, m. cricoarytenoideus posterior, m. cricoarytenoidus lateralis, m. thyroarytenoideus, m. aryepiglotticus…/*

The incidence of residual neuromuscular blockade (rNMB) remains unacceptably high, placing patients at risk of adverse outcomes, prolonged post-anaesthesia care unit PACU stay, and patient discomfort (Murphy et al., 2008).

Inadequate, insufficient reversal of muscle paralysis is responsible for early post-anaesthesia complications: hypoxia or/and respiratory acidosis owing to insufficient ventilation: decreased tidal volume - TV, increased respiratory rate - RR, noneffective secretion clearing and respiratory obstruction. Deficient coordination of upper and lower pharyngeal sphincter means a danger of pulmonary aspiration of saliva, blood or gastric content. The consequences are life threatening – hypoxaemia - decreased arterial oxygen pressure PaO_2, hypercarbia – increased carbon dioxide pressure $PaCO_2$, leading, when not counteracted, to cardiac arrest (Murphy et al., 2008).

Early respiratory effects of residual blockade if not quickly reversed may result in late complications e.g. pneumonia, atelectasis, with lung surface depletion and chronic respiratory insufficiency. Incidence of respiratory complications increases with patient's age. Clinical assessment is the most common means of assessing the return of patient strength, but these tests are inaccurate.

Table 2

Clinical Subjective Criteria	Reliability
Eye opening on demand	40%
Tongue protruding	55%
Loud speaking	47%
Sustained head lifting / at least for5 s/	51%
Sustained leg lifting for 5 s	50%
Sustained hand grip for	51%
Absence of dis-coordinated movements	70%

Most reliable clinical signs of paralysis reversal are summarised in Table III (Lucas et al., 2021).

Table 3

Clinical Assessment	
Oxygen blood saturation Sp O_2	≥ 95%
Tidal Volume	≈ 7 – 10 ml/kg
Inspiratory force	≥ - 30 - 50 cm H_2O
End tidal carbon dioxide pressure Et CO_2	≥ 45 mm Hg

(Eriksson, 2003)

Since 1997, according to Eriksson and Kopman, acceleromyography Train of Four – TOF is recommended to assess neuromuscular paralysis and blockade reversal.

The reaction of peripheral nerve stimulation /ulnar nerve or facial nerve/ is registered and reaction to fourth and first stimulation in form of pollex flexion or eyelid movement is compared (Kopman et al., 1997).

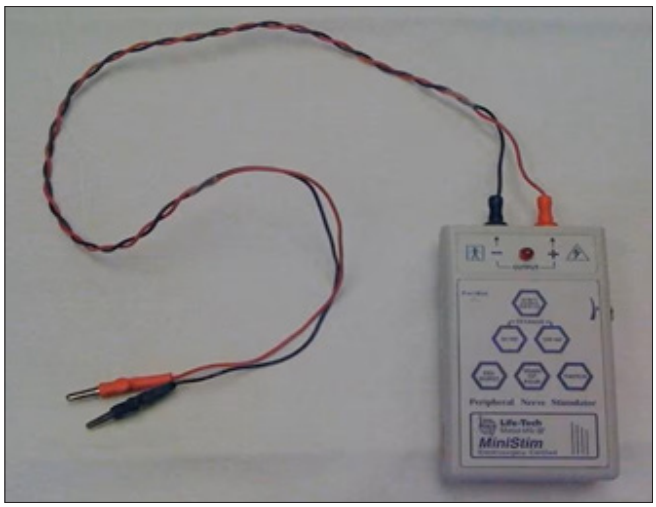


Figure 2: Nerve stimulator

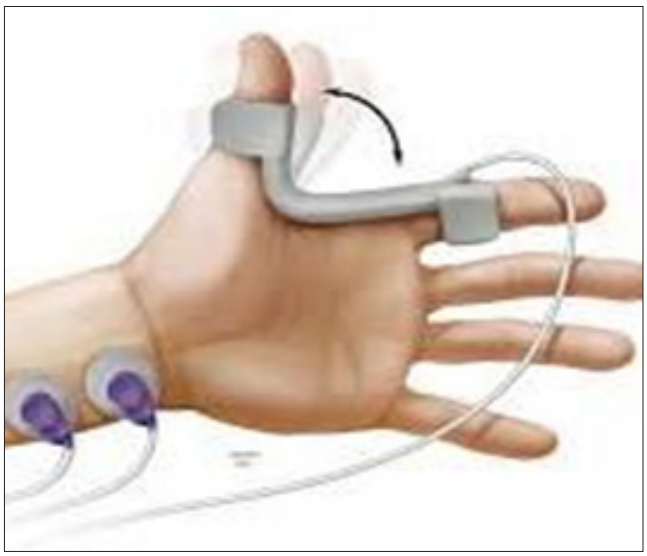


Figure 3: Ulnar Nerve stimulation

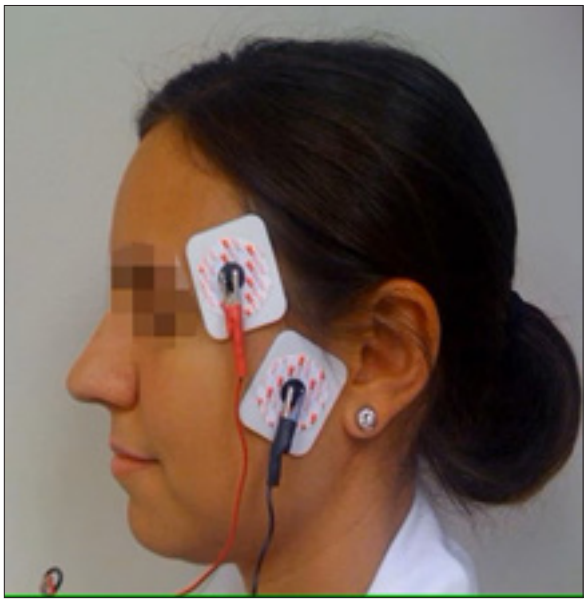


Figure 4: Facial nerve stimulation

Peripheral nerve stimulators are commonly available, but their use is not routine and the anaesthesiologists still rely on subjective assessment.

The ideal reversal agent

- should have a fast onset
- should be efficient at any time, even soon after paralyzing the patient
- should be able to provide complete reversal either for light or profound blockade
- should have a longer half-life than the muscle relaxants
- should not have any side-effects.

The skeletal muscle paralysis can be reversed by two types of drugs: acetylcholinesterase inhibiting drugs and selective relaxant biding agents SRBA.

The result of AChE inhibitors is stimulating nicotine receptors as a result of acetylcholine ACh increase in neuromuscular junction. But anticholinesterase drugs have potent muscarinic stimulating properties on the heart – slow heart rate, dysrhythmias, on bronchi – bronchoconstriction and secretion stimulation and on guts – enhaced peristalsis. This side effects can be mitigated by atropine (Claudius & Fuchs-Buder, 2020). AChE inhibitors time of action is long but is shorter than action of most popular non-depolarising muscle relaxants. e.g. half time T1/2: neostigmine 52 min, rocuronium 66-80 min, vecuronium 55- 81 min.

The recovery of muscle strength is related to depth of the blockade, so AChE inhibitors are not effective in deep muscle relaxation.

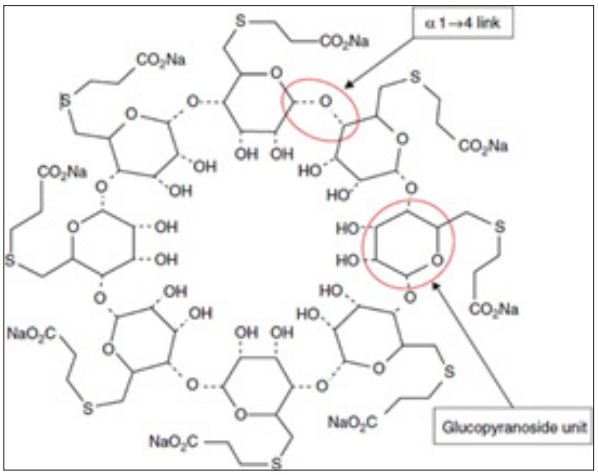
Rapid reversal of muscle paralysis is crucial in situations where maintaining paralysis is no longer necessary or could lead to life threatening complication:

1. Deep blockade when neither intubation nor ventilation is possible – cannot intubate CNI, cannot ventilate CNV, cannot oxygenate CNO
2. Surgeons demand after brain or spine injury when neurological assessment is required
3. Unpredicted end of operation
4. Prolonged paralysis after ambulatory procedure
5. Malignant hyperthermia suspected after muscle relaxing agent administration
6. Recurarisation in postoperative ward
7. In patients suffering of neurological and rheumathoid diseases affecting skeletal muscles - *polyneuropathia*

In 1996 L. H. Booij noticed that „ effective decrease of muscle relaxation in every moment is not possible". But fortunately for anaesthesia and all the patients in risk the revolutionary moment ensued soon (Sokół-Kobielska, 2013).

Cyclodextrins were well known at the end of XX century, being used in cosmetics to prolong life time of some agents. They are water soluble, bind steroids, are well tolerated and excreted by kidneys. The discovery in 1998 of encapsulation for reversal aminosteroid muscle relaxants was the result of

work by Bom, a research scientist at Newhouse Research Organon International, site in Scotland0 (Bom et al., 2001). In 1999 Borgh A, the researcher for Organon found that over 200 cyclodextrins can reverse muscle relaxation. The most effective occurred the modified cyclodextrin gamma containing eight side chains to extend encapsulating properties. The agent is known as *sugammadex* – su stands for sugar, *gammadex* stands for structural molecule γ-cyclodextrin. Experimental studies were performed in 2000 on guinea pigs, mice and monkeys. Soon started experimental studies on Organon workers volunteers (Bom et al., 2009). Clinical studies were initiated by Cameron and Gijsenbergh., The results were published in Anaesthesiology 2005 (Gijsenbergh et al., 2005).



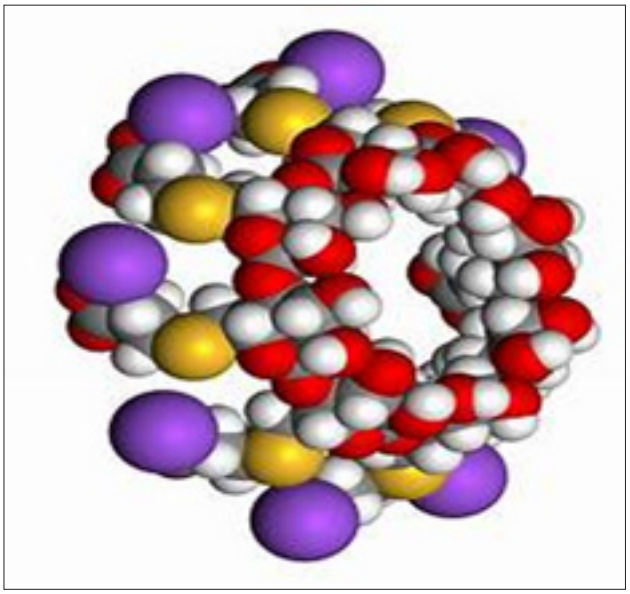


Figure 5: Structure of Sugammadex $C_{72}H_{104}Na_8O_{48}S_8$

Sugammadex does not bind to blood proteins, is not metabolised but almost in total /96 – 100%/ eliminated by kidneys. The volume of distribution Vdss is 11 – 14 litres, lower in children 3,1 l, blood clearance - Cl about 80 ml/min, /28 ml/min in elderly and in patients with mild renal impairment / half time of life T1/2 is 1,8 h, shorter - 0,9 h in children, longer – 6,1 h in elderly and in mild renal insufficiency (Yang & Keam, 2009).

The dosage of Bridion is from 1 to 16 mg/kg of body weight depending on the level of neuromuscular blockade to be reversed and on initial and supplemental doses D1, Ds of a muscle relaxant. The dosage is not dependent on the type of anaesthesia (Naguib, 2007).

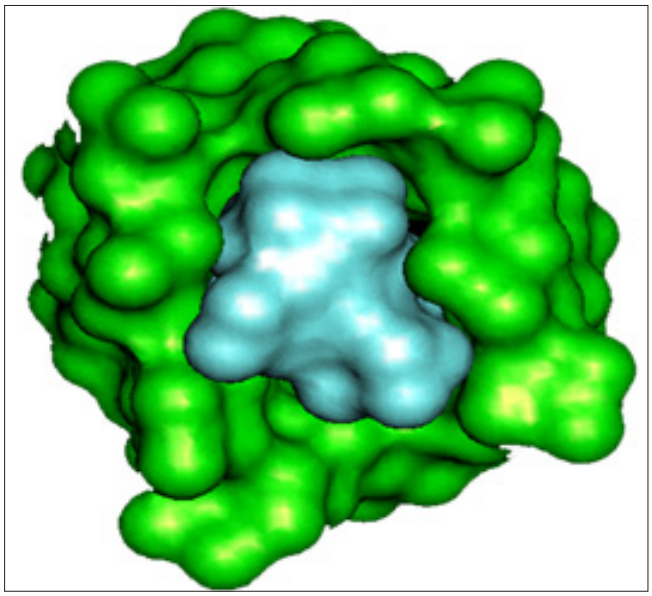


Figure 6 : BRIDION Makes a Trap for Rocuronium

The best moment to start reversal of neuromuscular blockade is when signs of muscle force recovery occur: tongue movements, asynchronization of breathing and when at least two or three switches of TOF are visible. Time to recovery to TOF ≥ 0,9 is closely related to the dose of BRIDION: Table IV /15/

Table 5 : SUGAMMADEX DOSE TIME to RECOVERY ToF ≥ 0,9

	Rocuronium dose 1,2 mg/lg
1 mg/kg	3 min
2 mg/kg	2 min
4 mg/kg	1 – 2 min
16mg/kg immediate recovery	1,5 min

Usual dose 2 mg is recommended. It is effective in in children 2 – 17 years of age, in overweight patients, in elderly, although time to full recovery may occur a little longer than in adults / Fig.5/, in mild to moderate renal impairment /GFR ≥ 40 ml/ min/, in nursing mothers; Bridion penetrates to mother's milk but is not absorbed in newborn's gastrointestinal tract (Nag et al., 2013).

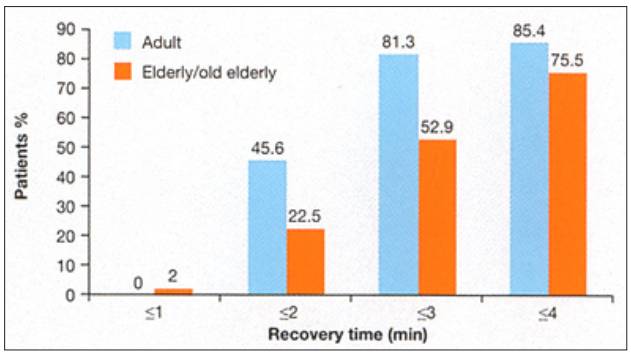


Figure 7 : Elderly vs adult patients
Rocuronium 0,6 mg/kg Bridion 2 mg/kg

Sugammadex is well tolerated healthy volunteers and in surgical patients. The tolerability profile of sugammadex was generally similar to that of placebo. The agent is not metabolised in humans. It exerts no influence on heart rate HR, blood pressure BP, histamine and acetylcholine release, renal and hepatic function. Sugammadex may theoretically interfere with some medical products e. g hormonal contraceptives - progestogen- lowering the free plasma concentrations. Some agents *toramifen*, *flucloxacilline*, *fusydine acid* may displace rocuronium or vecuronium from BRIDION. As a result recurrence of neuromuscular blockade might be observed (Nag et al., 2013). There are no known interactions between alcohol and Bridion.

The drug in clinical doses 1 – 4 mg/kg usually does not cause postoperative nausea and vomiting PONV, changes in blood coagulation (Stair & Fernandez-Bustamante, 2012).

Bridion should be not used in pregnancy as there is no data concerning influence on the foetus, in newborns and children under 2 years of age because of lack of observations on newborns' and young children mental and physical development, in severe renal failure GFR ≤ 30 ml/min,/18/ to reverse ester muscle relaxing drugs -atracurium, cis-atracurium (Sokół-Kobielska, 2013).

If re-administration of a muscle relaxant - rocuronium or vecuronium is required a waiting time of 6 -24 hours /3 x T1/2 / is recommended. If neuromuscular blockade is required before the recommended waiting time has passed, a nonsteroidal neuromuscular blocking agent - cis-atracurium, atracurium should be used (Sokół-Kobielska, 2013).

Hypersensitivity reactions have occurred in some volunteers. In clinical trials these reactions were reported uncommonly and the frequency is unknown. These reactions varied from isolated symptoms to serious systemic reactions (i.e. anaphylaxis, anaphylactic shock) and have occurred in persons with no prior exposure to sugammadex. Symptoms associated with these reactions can include: flushing, urticaria, erythematous rash, severe hypotension, tachycardia and swelling of tongue and pharynx (Nag et al., 2013).

In a study in volunteers doses of 4 mg/kg and 16 mg/kg of sugammadex resulted in maximum mean prolongations of the activated partial thromboplastin time (APTT) by 17-22% and prothrombin time INR by 11-22%. These prolongations were of short duration ≤ 30 minutes. No clinically relevant effect of sugammadex alone or in combination with anticoagulants on the incidence of peri- or post-operative bleeding complications was observed. An increased risk of bleeding cannot be excluded in patients: with hereditary vitamin K dependent clotting factor deficiencies, with pre-existing coagulopathies on coumarin derivates, at an INR above 3.5, on anticoagulants after a dose of 16 mg/kg sugammadex (Stair & Fernandez-Bustamante, 2012).

Sugammadex Bridion is not ideal but still deserves to be considered as a revolution in anaesthesia and benefit for patients. It should be more commonly used in clinical practice, In patients in poor general state - ASA III, IV, and in patients over 70 years old it should be the blockade reversing agent of choice. Elderly patients not infrequently suffer of chronic cardiovascular and/or pulmonary disease, are obese, diabetic, their muscle mass is significantly diminished. Residual blockade of neuromuscular transmission result in early and late complications; in elderly patients it is particularly dangerous and may be life threatening (Staals et al., 2008; Sokół-Kobielska; Pietraszewski & Gaszyński, 2013; Abrishami et al., 2010).

Bridion is also the agent to reverse muscular paralysis in mentioned above atypical clinical situations CNI CNV CNO cannot intubate cannot ventilate cannot oxygenate (de Boer et al., 2007; Pavoni et al., 2012; Jones et al., 2008; Sparr et al., 2007) on surgeons demand, at unpredicted end of operation.

When malignant hyperthermia is suspected after muscle relaxing agent administration in anaphylaxis induced by rocuronium (Jones & Turkstra, 2010; McDonnell et al., 2011) in patients suffering neurological and rheumathoid diseases affecting skeletal muscles (de Boer et al., 2009).

The incidence of residual neuromuscular blockade could be reduced to zero if sugammadex Bridion is used as the reversal agent and the correct dosage is selected with the use of neuromuscular monitoring. Rapid reversal and the reduction of postoperative residual paralysis may reduce the overall hospital costs and provide significant improvements in patient safety.

Quantitative neuromuscular monitoring devices are necessary to ensure appropriate dosing and adequate reversal of neuromuscular blocking agents.

Table 5

Ideal neuromuscular block reversal agent
• Can be used to reverse any neuromuscular blocking drug
• Can be used to reverse any depth of neuromuscular block
• A rapid onset of maximal effect - within a few minutes
• No adverse cardiovascular effects
• No adverse muscarinic effects
• No histamine release or risk of anaphylaxis
• Not dependent on organ elimination
• No ceiling effect
• Available as a solution

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