Sugammadex — indications and clinical use

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ABSTRACT

Neuromuscular blocking agents are a substantial element of anaesthesia in almost every surgical field. Nevertheless, their use has been associated with rise in mortality and morbidity. Of importance are: the general health state of the patient, liver and renal function, metabolism and excretion, active metabolites, side effects of muscle relaxants and, above all, residual paralysis. Prophylaxis of insufficient block reversal consists of blockade monitoring using acceleromyography and pharmacologic reversal of blockade. An ideal antagonistic agent should be characterised by rapid and complete reversal of blockade, disregarding its depth and total dose of muscle relaxant, lack of side effects and 100% excretion. These criteria are met by cyclodextrine gamma — sugammadex. In kontrast to anticholinergic agents, which enhance the acetylcholine amount in the postsynaptic part of the neuromuscular junction, sugammadex encapsulates myorelaxing agent removing it from the junction. Sugammadex binds specifically only muscle relaxants of aminosteroid structure. In this paper, we present the current understanding of the characteristics, dosing, indications and side effects of sugammadex.

Key words: neuromuscular blocking agents, sugammadex; neuromuscular blockade, monitoring; neuromuscular blockade, residual block

D-tubocurarine was isolated by King in 1940 and introduced into clinical practice by Griffith and Johnson in 1942, representing a real breakthrough in the development of anaesthesiology [1]. Since that time, neuromuscular blocking agents have become crucial in anaesthetic management in all fields of surgery, facilitating the induction and maintenance of anaesthesia. However, their use has been associated with an increased risk of side effects and life-threatening events.

The widespread use of muscle relaxants has resulted in a six-fold increase in the number of deaths and complications during the early postoperative period [2]. The contributing factors include the patient’s general medical status, liver and kidney function, the elimination of agents, the presence of active metabolites, side effects (e.g., hypersensitivity reactions), and, most importantly, the insufficient reversal of the muscle relaxations (residual block). The residual block causes early complications following anaesthesia using neuromuscular blocking agents, such as airway obstruction, respiratory failure and aspiration of saliva, blood or gastric content [3, 4].

The diaphragm, upper oesophageal sphincter, inferior pharyngeal constrictor and aryepiglottic muscles are particularly susceptible to residual block. The lack of coordination of the upper oesophageal and pharyngeal sphincters is responsible for the risk of aspiration. Residual blockade cannot be detected based on objective clinical markers [5] (Table 1).

The effects of inadequate neuromuscular junction blockade can be prevented by using short- and intermediate-acting muscle relaxants, avoiding substances with biologically active metabolites, monitoring the resolution of muscle relaxation based on acceleromyography (train-of-four, double-burst stimulation) and using antagonists for pharmacological reversal of relaxation [6].

An ideal antagonist should present fast and full reversal of relaxant effects, regardless of the dose and degree of blockade, lack of side effects, and complete excretion from the body [7].

The non-depolarising neuromuscular block is antagonised by cholinesterase inhibitors and selective relaxant binding agents [8].
Cholinesterase inhibitors act competitively by inhibiting the breakdown of acetylcholine and increasing its concentration on the post-synaptic side of the neuromuscular junction; however, its release is not increased, and the time of action of the inhibitor can be shorter than the relaxant, which remains in the pre-synaptic region until complete elimination. Anti-cholinesterase agents are not effective for deep blocks; administered in high doses, they may cause acetylcholine blockade.

The mechanism of action for cyclodextrins is different. Cyclodextrins are water soluble ring complexes of glucose particles that selectively bind to aminosteroid relaxants. The most potent effects are exerted by g-cyclodextrin or sugammadex [9].

**CHARACTERISTICS OF SUGAMMADEX**

Sugammadex contains 8 glucose molecules with negatively charged side chains. The ring with a lipophilic interior binds to aminosteroid relaxants with a 1:1 ratio, removing the relaxant from the neuromuscular junction. The resultant complex lacks relaxing properties and is excreted within 24 h via the kidneys (96%) and expiration and faeces (0.02%). The remaining part is slowly decomposed in the liver; only 1 of 25 million sugammadex-rocuronium complexes is dissociated [10, 11].

Sugammadex is characterised by molecular weight (2,178 Da, pH 7.5), osmolality (300–500 mOsm L⁻¹), distribution volume (11–14 L), clearance (88 mL min⁻¹), and elimination half-life (1.8 h). The drug was not demonstrated to affect haemodynamic parameters, respiration, blood clotting or thermoregulation [12]. The high dose used in volunteers (up to 96 mg kg b.w.⁻¹) did not cause an adverse reaction [13].

Sugammadex shows had the highest affinity for rocuronium, then vecuronium and the lowest for pancuronium.

**RECOMMENDED DOSE**

Based on an objective assessment of the depth of neuromuscular block, the following doses of sugammadex have been recommended:

- 2 mg kg⁻¹ when relaxation has subsided by at least 25% (2 TOF responses, TOFI 25),
- 4 mg kg⁻¹ for a deep block when the PTC is 1–2 or when the features of neuromuscular blockade return after a dose of 2 mg kg⁻¹,
- 16 mg kg⁻¹ for a complete block when the relaxant effects have to be reversed quickly.

The dose does not have to be modified in the elderly or obese (BMI 24–30 kg m⁻²) patients, those with mild or moderate renal failure (Cl.Crea > 20–30 mL min⁻¹), mild or moderate hepatic failure, breast-feeding mothers or children aged 2–17 years.

In patients with morbid obesity (BMI > 30 kg m⁻²), the dose of sugammadex should be calculated according to an adjusted or even ideal body weight [14].

The time of neuromuscular block resolution, or the return of muscular strength (TOFI > 0.9) after sugammadex, ranges from 1 to 5.9 min, depending on the baseline degree of relaxation [15–17]. The dose calculated for a particular patient should be administered in a bolus injection. Continuous infusions should not be used due to a high molecular weight (> 2,000 Da) because cyclodextrin accumulating in the renal tubules can inhibit their secretory capacity [18].

**ADVERSE SIDE EFFECTS**

Studies in healthy volunteers and long-term clinical experience have confirmed that sugammadex is a safe drug. The reported adverse side effects are rare and mild [19]:

- a reduction in drug clearance to 28 mL min⁻¹ in elderly patients and those with impaired kidney function,
- a slight delay in neuromuscular block reversal in elderly patients and those with circulatory failure,
- a transient prolongation of the QT interval to > 500 ms in patients anaesthetised with sevoflurane or propofol (the direct effects of sugammadex are doubtful as no adverse effect of the drug administered at an extremely high, supraclinical dose of 32 mg kg⁻¹ on the bioelectrical activity of the heart has been demonstrated [20],
- allergic reactions, such rash, erythaema, or bronchospasm (although no relationship with sugammadex has been shown, their incidence is comparable to individuals receiving placebo; also, due to the low number

<table>
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<th>Table 1. Clinical and objective criteria for residual block assessment</th>
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<td><strong>Clinical criteria</strong></td>
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<td>Eye opening to verbal command</td>
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<td>Expectoration</td>
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<td>Tongue protruding</td>
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<td>Loud speaking</td>
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<td>Movement of all four limbs</td>
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<td>Head/lower limb raising for 5 sec</td>
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<tr>
<td>Hand shaking</td>
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<td>Tongue depressor test</td>
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Elżbieta Sokół-Kobielska, Sugammadex in clinical practice
of glucose molecules in cyclodextrin, the compound is much safer than multimolecular dextran),
— a short-term (< 30 min) prolongation of activated partial thromboplastin time (APTT) following doses of 4 and 16 mg kg$^{-1}$,
— a metallic or bitter taste, especially after high doses, oral dryness,
— displacement interactions (some drugs e.g., toremifene, flucloxacillin, fusidic acid) “compete” for rocuronium binding with sugammadex, and after the reversal of relaxation, the degree of neuromuscular blockade has to be monitored; thus, such drugs should not be administered within 6 hours preceding anaesthesia), and
— uptake reactions (steroid drugs e.g., hormonal contraceptives) can bind to sugammadex, thus decreasing its efficacy in reversing the effects of muscle relaxants).
Sugammadex is not recommended in cases of severe hepatic failure and severe renal failure when the creatinine clearance is < 30 mL min$^{-1}$. The complex with a muscle relaxant can be eliminated from the body using haemodialysis.
The drug in question is not absorbed after oral administration. Its use during the first trimester of pregnancy, in newborns, infants and children younger than 2 years of age is still limited due to insufficient experience. Most likely, the drug does not pass into maternal milk.

**PHYSICAL INCOMPATIBILITIES**
Sugammadex is incompatible with drugs that directly affect serotonin type 3 receptors (ondansetron and other drugs in this group), ranitidine and verapamil. Therefore, these drugs should not be mixed but injected after thorough rinsing of the intravenous line [21].

**INDICATIONS**
The emergency use of sugammadex is indicated in the cases when immediate reversal of neuromuscular block is required (“cannot intubate, cannot ventilate”), when the block has not subsided although the time of action consistent with the pharmacodynamics of the relaxant has elapsed or when block reversal is not achieved despite the administration of a cholinesterase inhibitor.

The non-emergency use of sugammadex is indicated in individuals who require the quick recovery of full motor skills, including elderly patients, those with morbid obesity or a respiratory disorder and children.

The general recommendations for sugammadex include the following:
— “difficult airway” cases, including difficult laryngoscopy and intubation and difficulties in lung ventilation through a face mask [22],
— a overdose of the muscle relaxant,
— a long surgical procedure requiring a high total relaxant dose,
— the muscle-relaxing effects of vecuronium or pancuronium metabolites
— administration of the relaxant immediately before the completion of anaesthesia,
— early completion or cancellation of surgery after the induction of anaesthesia,
— intraoperative hypothermia [23], or
— risk of aspiration of gastric contents, blood, saliva, or mucus, including:
  ▪ intake of food products or liquids shortly before the procedure,
  ▪ obstruction of the gastrointestinal tract,
  ▪ nose and throat surgery,
  ▪ endoscopic pituitary procedures,
  ▪ 2nd and 3rd trimesters of pregnancy,
  ▪ obstetric procedures [24],
  ▪ morbid obesity [25], or
  ▪ history of bariatric surgery [26].
The detailed recommended indications are as follows:
— diseases that reduce airway patency, respiratory surface, or gas exchange, such obstructive and/or restrictive lung disease, asthma, pulmonary emphysema, and mediastinal tumours [27],
— anaesthesia in the elderly, newborns, or infants (Sugammadex has been used in 25-day-old infants and premature and full-term newborns) [28]. The decision to use an off-label drug in this age group is made individually after considering the benefits and risks),
— neuromuscular diseases (myasthenia, polyneuropathies, trauma, stroke-associated paralysis and paresis, or neuromuscular dystrophy) [29],
— the need for intraoperative reversal of neuromuscular block (i.e., neurophysiological monitoring during the following:
  ▪ ear surgery to identify the facial nerve (VII cranial nerve),
  ▪ parotid gland surgery to identify the facial nerve,
  ▪ thyroid surgery to identify the recurrent laryngeal nerve,
  ▪ stereotactic surgery in epilepsy,
  ▪ laminectomy for intervertebral disc herniation and spinal procedures where monitoring of the myogenic motor evoked potentials is needed to eliminate the risk of spinal cord ischaemia and resultant paresis [30, 31] (total or partial reversal of relaxation is recommended to obtain 2 responses during train-of-four stimulation; in partial reversal, the dose of sugammadex ranges from 0.125 to 0.5 mg kg$^{-1}$).
— recurarisation after the previous surgical procedure,
— ophthalmic surgery in children, 
— surgeries within the nose, throat, or larynx surgery, 
— operations with insertion of intermaxillary traction, perimaxillary inflammation, and abscesses of the oral cavity and throat limiting mouth opening and upper airway diameter [32],
— anaesthesia in mentally and physically disabled patients (dementia, Alzheimer’s disease, Down’s syndrome, deaf or mute individuals),
— treatment of severe laryngospasm (the administration of rocuronium instead of suxamethonium to abolish laryngospasm is safer; the subsequent use of sugammadex ensures the complete reversal of relaxation [32]),
— anaphylaxis after rocuronium (by binding to the muscle relaxant, sugammadex eliminates the cause of the hypersensitivity reaction [33]),
— lack of proper postoperative surveillance, or 
— transport of the patient to a remote ward or outside the hospital where the surgery was performed.

Sugammadex does not reverse the action of succinylcholine and benzylisoquinoline relaxants. Moreover, sugammadex is not effective in cases of prolonged weakness of skeletal muscles after long-term relaxation in the intensive care unit and does not abolish muscle spasms during tetanus or electrolyte abnormalities.

When re-relaxation is required within 24 h of the administration of sugammadex, benzylisoquinoline agents or suxamethonium should be used. An aminosteroid muscle relaxants can be repeated after 24 h. Using rocuronium with the maximum dose of 1.5 mg kg⁻¹ or even the average relaxing dose of 0.6 mg kg b.w.¹ is admissible, once the threelfold elimination half-life has elapsed (i.e., 6 h after the first administration of sugammadex) [34].

Monitoring of the degree of relaxation by train-of-four stimulation helps to specify the indications for sugammadex use and determine the desired dose.

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