Sugammadex: What to Know for Your Daily Practice

MIRELA TIGLIS[1], IOANA CRISTINA GRINETESCU[1,2], TIBERIU PAUL NEAGU[3,4]*, FLAVIA LILIANA TURCU[5,6], ANDRA MARIA COCOLOS[7,8], IOANA MARINA GRINETESCU[1,2]

[1] Emergency Clinical Hospital of Bucharest, Department of Anesthesiology and Intensive Care, 8 Calea Floreasca, 014461, Bucharest, Romania

[2] Carol Davila University of Medicine and Pharmacy Bucharest, Clinical Department No. 14, 8 Eroii Sanitari Str., 050474, Romania

[3] Carol Davila University of Medicine and Pharmacy, Clinical Department No. 11, 8 Eroii Sanitari Str., 050474, Bucharest, Romania

[4] Emergency Clinical Hospital of Bucharest, Department of Plastic Surgery and Reconstructive Microsurgery, 8 Calea Floreasca, 014461, Bucharest, Romania

[5] Carol Davila University of Medicine and Pharmacy Bucharest, Clinical Department No. 3, 8 Eroii Sanitari Str., 050474, Romania

[6] St. John Emergency Clinical Hospital, Department of Nephrology and Dialysis,13 Vitan Barzesti Road, 042122, Bucharest, Romania

[7] Carol Davila University of Medicine and Pharmacy Bucharest, Clinical Department No. 2, 8 Eroii Sanitari Str., 050474, Bucharest, Romania

[8] C.I. Parhon National Institute of Endocrinology, Department of Endocrinology, 34-36 Aviatorilor Blvd., 011863, Bucharest, Romania

Sugammadex (Bridion) represents a class named muscle relaxant encapsulator. It can be used to reverse the neuromuscular blockade induced by rocuronium or vecuronium in case of general anesthesia. Its molecular weight is 2.178 g/mol, with a structure consisting in a ring of eight negative charges. It has no receptor interaction in human body and it is eliminated via kidney, being contraindicated in end-stage kidney disease patients. Sugammadex has few side effects but there are same case reports about allergic reactions. Only three drugs can actually interact with sugammadex: toremifene, flucloxacillin and fusidic acid. It can be used in elderly and pediatric patients, in morbidly obese patients, patients with hepatic insufficiency or mild and moderate renal insufficiency or in muscular disease. Despite its beneficial use, the high price remains its main issue.

Key words: sugammadex, muscle relaxants, postoperative-residual-neuromuscular-block, renal failure

Sugammadex is the only representative of a drug class called steroidal muscle relaxant encapsulators. Its clinical use was approved in Europe in 2008, in Japan in 2010, in 2015 in United States (US) and in 2016 in Canada. Nowadays, there are over 60 countries who use it and there are approximately 18 million patient exposures per year.

It is one of the most expensive compound used in anesthesia, one vial of 2 milliliters containing 200 milligrams costs varies from 40 to 180 euros depending on contract agreements between the suppliers and different hospitals. Anesthesia societies and anesthesia providers are trying to create and implement some algorithms to detect and treat postoperative residual neuromuscular block (RNMB) in order to define those situations where it is economically and medically desirable to use sugammadex [1]. RNMB may cause especially impaired upper airway function, respiratory insufficiency, increase the risk of aspiration and the postoperative pulmonary complications [2].

The modern concept of balanced anesthesia include neuromuscular block to obtain immobility for airway management and surgical exposure, termination on its effect being associated with side effects of acetylcholinesterase inhibitors. Muscle relaxants are divided into depolarizing (succinylcholine) and non-depolarizing (steroid based and benzylisoquinoline) muscle relaxant (NDMB). Even though NMB have fewer adverse effects (especially allergic reactions) during anesthesia, they may cause a residual duration of action of muscle relaxants in some subjects leading to RNMB (its incidence is around 20-25%).

* email: dr.neagupaul@gmail.com; Phone +4021.599.23.00

Until 2008, there were three scenarios to prevent RNMB: 1) not to use muscle relaxants, 2) wait until complete metabolism and fully recover of muscle function or 3) antagonize the effect of muscle relaxant with cholinesterase inhibitor (e.g. neostigmine) [3]. Not long ago, the NDMR action could only be reversed by acetylcholinesterase agents. It briefly inactivates acetylcholinesterase and increases the amount of acetylcholine at the postsynaptic membrane. The problem with neostigmine is that even after a train-of-four (TOF) – count of 4, there is no guarantee of fully recovery even with the maximal approved dose [1]. Thereby, sugammadex, a molecule that can reverse any depth of neuromuscular block, even if it is administered 3 minutes following a 1.2 mg/kg dose of rocuronium [4], has changed the perspective of anesthesia practice. It is the key in a can`t ventilate, can't intubate situation [4].

The purpose of this paper is to bring up-to-date information regarding the sugammadex, to summarize its main pharmacological characteristics and to present the most important aspects than we can use in our daily practice, especially in some particular situations like RNMB, difficult airway management or in some subgroups of patients.

The history of sugammadex

The gamma-cyclodextrin, with a ring structure of eight linked alpha-1,4 glucopyranose units and a central cavity, was discovered in 1935 by FREUDENBERG, K. and JACOBI, R. [5]. The cyclodextrins are a group of oligosaccharides that have a large number of hydroxyl groups. The cyclic

structure forms a cavity with a water-soluble hydrophilic exterior and a hydrophobic interior being capable to encapsulate lipophilic molecules. The gamma-cyclodextrin has a cavity with a diameter of 7.5-8.3 A. The cavity diameter limits the size of the molecules that can be encapsulated, the encapsulation process being extremely fast.

After the discovery of the synthesis pathway, the mass production of cyclodextrins started. They were first used as solubilizers and then, FREUDENBERG, K. and JACOBI, R. [5] obtained the patent for the drug formula. Nowadays, the cyclodextrins are found in the composition of many lipophilic drugs for increasing their water solubility, like dexamethasone, cephalosporins, propofol, etomidate, bupivacaine, piroxicam, nitroglycerin, nicotine, omeprazole, diclofenac etc. Cyclodextrins are used as stabilizers and solubilizers, especially in the food and cosmetic industries [6].

First studies with modified cyclodextrins were performed in mice by blocking the phrenic nerve with rocuronium and concluded that the reversal potencies depends on the cavity size, with the gamma-cyclodextrins having the highest potency [7]. It was shown that sugammadex produced a dose-dependent neuromuscular block reversal [8]. A large number of compounds were further studied both in vitro and in vivo. A new compound from gamma-cyclodextrin derivatives was selected for its high affinity and received the generic name of sugammadex [9] being the first selective and efficient agent to antagonize the effect of non-depolarizing neuromuscular-blocking drugs.

Using nuclear magnetic resonance spectroscopy with single crystal X-ray analysis, it has been demonstrated a one on one binding between rocuronium or vecuronium and sugammadex [10]. It was observed that all four rings of the steroid nucleus were in contact with the lipophilic wall of the sugammadex cavity [10].

Toxicity and side effects

Due to the fact that between sugammadex and aminosteroidal non-depolarizing neuromuscular-blocking agents there is a chemical interaction with no receptors implication, adverse violent side effects are not to be expected [10]. Typically, the side effects are related with the fast recovery of the muscle function during balanced anesthesia: coughing, uncontrolled movement or grimacing [11].

In literature, there are few cases of allergies against sugammadex which starts in about 5 minutes after administration [12]. The allergic rate is about 1:34.483 patients from 3 years of data reported in Japan [13].

Until today, there are no clinical evidence about the use of sugammadex in pregnant women. Animal studies in pregnant rats have shown no side effects on fetus, birth or postnatal development [14]. Nevertheless, the oral absorption is very low [11].

There are same case reports about the influence of sugammadex over cardiac function [15], but the QT-prolongation and atrioventricular blocks may be cause by other factors during the general anesthesia or increased by associated chronic pathologies [16,17].

In some cases chest wall rigidity and negative pressure pulmonary edema was described following sugammadex administration [18,19].

Sugammadex seems to produce a temporary effect (less than 60 min) on coagulation parameters by activating the partial thromboplastin and the prothrombin time but some randomized trials (in over 1100 patients) has shown no risk of bleeding [20].

About the central effect of sugammadex, the blood-brain barrier penetration in rats is under 3% and no pertinent central toxicity was discovered [21]. Some questions raises about the effects on patients with impaired blood-brain barrier (e.g. trauma, intracranial bleeding, sepsis, Alzheimer's disease) because in cell culture, important doses of sugammadex have caused neuron death by apoptosis or necrosis [21].

The studies reveal that the daily intake of gamma-cyclodextrins with food is about 4 grams per person with a maximum of 8.8 g per person per day and that such amounts are safe and have low toxicity [22].

It seems that sugammadex has an affinity for bone and it binds to hydroxyapatite skeletal bone and teeth [22]. In experimental studies, there was found a prolong retention especially in long bones and it is not yet understood its effects on bone remodeling or if it influences the periosteum integrity [23,24]. Sugammadex interfere with enamelization of teeth.

All the toxicological studies performed in rats has shown that daily intravenous administration of 120-200 mg kg^{-1} causes no adverse effects, even if larger doses like 600-630 mg kg^{-1} produce only a biochemical response, there are no side effects [25].

A dose of 4 mg/kg of sugammadex exhibited no side effects on progesterone or cortisol levels, instead it was related with a temporary increase in aldosterone and testosterone amount and during repeated exposure it may produce some sexual dysfunction or prostatic hyperplasia [26,27].

In case of allergy against rocuronium, sugammadex was not able to stop the allergic reaction once it was triggered in some experimental studies. There are some case reports where high dose of sugammadex were efficiently used in this situations [1].

Clinical pharmacology

Sugammadex is a modified and the most powerful gamma-cyclodextrin derivative, very soluble in water, with a circular structure with eight adjoining glucose molecules, used to reverse the effects of non-depolarizing neuromuscular-blocking drugs and should not be used to antagonise the blockade induced by nonsteroidal neuromuscular blocking agents like succinylcholine or for steroidal neuromuscular blocking agents other than rocuronium or vecuronium. Its molecular weight is 2,178 Daltons, with a structure consisting in a ring of 8 negative charges [28] Sugammadex has no effect on intrinsic biological activity.

When it is released in the bloodstream, there are free molecules of rocuronium which are in equilibrium with the tissues and are rapidly captured by sugammadex molecules, thus, the plasma free rocuronium level decrease immediately.

Sugammadex sequesters the free molecules of the muscular relaxant which leads to a decreasing concentration with a rapid offset of neuromuscular block due to liberation of acetylcholine for the prejunctional and postjunctional nicotinic receptors which are sensitive to acetylcholine. It encapsulates the whole steroid skeleton of the aminosteroidal non-depolarizing neuromuscular-blocking drugs creating a concentration gradient favoring the movement of rocuronium or vecuronium from neuromuscular junction into the plasma and so decreasing its free concentration in the central compartment [28].

The molecules of rocuronium or vecuronium fits into the cavity of the sugammadex ring, forming a one to one complex. This complex is not metabolized due to the lack

of the required enzymes for cyclodextrins and it is eliminated nearly 100% via the kidney, with a clearance of approximately 70-120 mL/min, equal to the normal glomerular filtration rate [29,30], as it was demonstrated in studies on the guinea pig [31]. It is not well known how sugammadex elimination time is influenced by antidiuretic drugs [32]. Even if the mechanism of action of sugammadex is fully independent of renal perfusion, only 29% of the sugammadex-rocuronium molecules can be cleared over 72 hours in an end-stage kidney disease [33]. Due to the renal elimination, it is not indicated in patients with creatinine clearance below 30 mL/min or in patients who are enrolled in the chronic dialysis program, especially peritoneal dialysis patients [1,34]. So far, there was no case reporting relapse neuromuscular blocking in renal failure patients [35]. However, the molecules of sugammadex can be dialyzed with normal dialysis filter [35,36].

Rocuronium has an affinity binding three times greater than vecuronium for sugammadex. This is characterized by a high association rate and low dissociation rate. The constant of association equilibrium (association-dissociation ratio at equilibrium) values of sugammadex for rocuronium is 25.10^6 Mol^{-1} and for vecuronium is 10.10^6 Mol^{-1}. The concentration of sugammadex should exceed the rocuronium concentration to ensure that the majority of rocuronium molecules are encapsulated [37].

The effect of sugammadex on benzylisoquinoline group (e.g. mivacurium or cisatracurium) is very low, and, in order to reverse the neuromuscular blockade induced by pancuronium, higher doses are required. It has no effect on nicotinic or muscarinic receptors [38]. Sugammadex has a small volume of distribution with a short elimination half-life [11]. Its elimination half-life is about 100-150 minutes [38].

Dosage

The most important aspect is that the dose of sugammadex depends on the depth of neuromuscular blockade and it is very important to have objective neuromuscular monitoring [37]. At a dose of 1-2 mg/kg intravenously administered, sugammadex reverse the rocuronium-induced muscle blockade (dose of 0.6 mg/kg) quickly and efficiently producing 90% recovery of muscle contraction within 3 min. In some animal studies there were used 10 times the usual dose (up to 10 mg/kg intravenously) and no modifications in hemodynamic parameters were observed during or after the administration [9]. Therefore, it allows a much rapid postoperative discharge, aspect that can be important for patients with deleterious health conditions, elderly patients, patients with malignancy etc [38,39].

The vecuronium-induced neuromuscular block is less reversed by sugammadex being required a dose of 2 mg/kg [4]. For a profound neuromuscular-blockade produced by 0.6 mg/kg dose of rocuronium, it is needed a dose of 4-8 mg/kg sugammadex with a mean recovery time of 3 min [9]. Immediate reversal of a dose of 1.2 mg/kg rocuronium requires a dose of 16 mg/kg sugammadex with a mean recovery time of 1.5 min [40]. There are some studies with doses up to 96 mg/kg sugammadex used in healthy adult patients that presented no adverse effects [41].

There are many studies that compare both efficacy of neostigmine 50 mg/kg with glycopyrrolate 10 mg/kg) and sugammadex 2 mg/kg to antagonise the neuromuscular blockade induced by rocuronium. Mean time to a TOF (train-of-four) ratio recovery of 0.9 (it is generally accepted as a threshold of adequate muscular recovery was about 1.5 min for sugammadex and 18.6 minutes for the neostigmine/glycopyrrolate combination [42]. Another important aspect is that increasing the dose of sugammadex allows us to antagonize even a deep neuromuscular block with the same efficacy and this cannot be said about neostigmine [42].

Drug interactions

In the latest studies, over 300 drugs used in current anesthesia practice, there are only three drugs that can interact with sugammadex [43]. The first one is toremifene (an oral estrogen-receptor modulator used to treat metastatic breast cancer). Flucloxacillin (a B-lactam penicillin) is the second one and the last one is fusidic acid (a steroidal bacteriostatic agent). Patients who use this type of drugs might experience a delayed recovery from the neuromuscular block.

Some drugs, like aminoglycosides and magnesium potentiate the effect of muscle relaxant agents and may require a larger dose of sugammadex to impede their effects [3].

Sugammadex appeared to have an effect on several endocrine disorders [44,45]. One bolus of it is considered to be equivalent to one missed dose of progesterone [10].

Clinical consideration

There are some particular subgroups of patients where sugammadex administration should be carefully considered in our daily practice:

-Elderly patients

In this subgroup of patients, recovery time from the neuromuscular bock is extended from < 2 min to < 4 minutes but the advocated doses are the same as for adults [11,46].

-Pediatric patients

Sugammadex is only accepted in children older than 2 years and for reversal of a moderate (TOF count of > 2) neuromuscular blockade at a dose of 2 mg/kg. Studies has shown that it is well tolerated in pediatric patients but have a more rapid onset time [47]. A cohort study made by Alonso et al. revealed that sugammadex can be used in neonates (the study included 23 neonates, 8 patients being one-day-old) [48]. There were found no significant adverse events and, compared with neostigmine, sugammadex had a low incidence of bradycardia.

-Obese patients

It is well known that in obese patients the muscle relaxants are administered in conformity with the ideal body weight but there are studies which demonstrate that a dose of 2 mg/kg ideal body weight failed to reverse deep and moderate neuromuscular blockade in morbidly obese patients [49]. Dose regimens adapted to ideal body weight plus 40% (adapted to corrected body weight) was effective in this subgroup of patients [49]. Neuromuscular monitoring is required in these cases [1].

-Patients with renal disease and liver failure

Molecules of rocuronium can be detected even after 7 days from the use of sugammadex in renal failure patients [4]. There are no available data about the pharmacokinetics presentation of sugammadex or if it can aggravate the renal status in this patients [50-53]. Data about the use of sugammadex in patients with hepatic failure are limited. Studies have shown that, since sugammadex modifies the metabolic pathway of rocuronium molecules from hepatic metabolization to unmodified renal excretion, a dose of 2 mg.kg of sugammadex is effective [54].

-Electroconvulsive therapy

General anesthesia, including complete muscle relaxation, is required in this situation. Three studies have

demonstrated the efficacy of rocuronium-sugammadex combination, recording fewer adverse effect of the therapy, like headache and myalgia [55].

-Patients with myasthenia gravis and other myopathies

The use of rocuronium-sugammadex mixture seems to be safe and efficient in this patients, under strict neuromuscular monitoring [56]. For others myopathies (myotonic dystrophy, Duchene disease, Becker's disease, spinal muscular atrophy, amyotrophic lateral sclerosis etc), there are case reports where sugammadex was successfully used after general anesthesia with rocuronium as a muscle relaxant [1,57].

Conclusions

Sugammadex is the only representative of a new class called steroidal muscle relaxant encapsulators and it has only few contraindications (e.g. allergy to sugammadex, end-stage kidney disease). For safely use, a quantitative neuromuscular monitoring is crucial. It is net superior to neostigmine because it rapidly and efficiently reverse RNMB. A lot of case reports have found that sugammadex is safe for neuromuscular block reversal for patients with important comorbidities. If sugammadex is used in doses accordingly with the neuromuscular monitoring, there should not be any problems regarding its efficacy. It is one of the most expensive drug used in daily general anesthesia, at a mean price of 100 euros per vial which is the main issue of this drug. Despite that, sugammadex remain the golden standard in cannot intubate, cannot ventilate situation after rocuronium administration and if it becomes daily available, rocuronium can be used as an alternative for suxamethonium, therefore, avoiding its side effects (e.g. fasciculations, myalgia, hyperkalemia, malignant hyperthermia etc). There are still many aspects to be taken into account, especially the use of sugammadex in neonate patients, the effect on brain trauma patients and the need to define those situations where it is economically and medically indicated to use sugammadex.

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