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BRIEF REPORT

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Sugammadex: An Update

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Abstract

The purpose of this update is to provide recent knowledge and debates regarding the use of sugammadex in the fields of anesthesia and critical care. The review is not intended to provide a comprehensive description of sugammadex and its clinical use.

Keywords: muscle relaxants, aminosteroidal group, reversal, neostigmine, sugammadex

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Introduction

Sugammadex is used to reverse neuromuscular blockade produced by the aminosteroid neuromuscular blocking drugs rocuronium, vecuronium and pancuronium [1] through encapsulation and inactivation of these muscle relaxants. It is a gamma-cyclodextrin, consisting of oligosaccharides linked around a central cavity. The muscle relaxant becomes entrapped within this cavity within a short time after sugammadex administration, neutralizing the relaxants, decreasing their plasma level and creating a concentration gradient between the neuromuscular end plate and plasma. This gradient causes displacement of the muscle relaxant from the end plate back into the plasma and further neutralization of the remaining relaxant. This mechanism of action explains the rapid reversal effect of sugammadex. In contrast to neostigmine, sugammadex can, through this unique mechanism, reverse even deep muscle relaxation, in a dose-dependent manner.

Why prefer sugammadex?

Sugammadex is devoid of the muscarinic side-effects of neostigmine. Its reversal effect is more predictable and, as previously stated, can reverse even deep blocks. Residual paralysis (curarization) may increase postoperative respiratory morbidity by impairing coughing, swallowing and the patients' ability to breathe deeply. Residual paralysis occurs more frequently with neostigmine than with sugammadex.

In a recent prospective, multicenter study [2] of the incidence and severity of residual paralysis following surgery, residual curarization (a TOF ratio<90%) was detected by the accelerographic method (TOF-Watch®), immediately before extubation and upon patient's arrival at the Post Anesthesia Care Unit (PACU). In this study, rocuronium was used in 99% of patients and neostigmine was used for reversal in 74% of patients, with the remaining patients not receiving any reversal agent. The incidence of residual paralysis was 63.5% at the point of tracheal extubation and 56.5% at the point of arrival at the PACU. The authors concluded that residual paralysis is common at the time of tracheal extubation and arrival at the PACU, despite using qualitative neuromuscular monitoring and neostigmine. It was concluded that more effective detection and management of neuromuscular block is needed to reduce the risks associated with residual curarization.

What do we know about the incidence of residual paralysis after sugammadex reversal? In a recently pub-

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lished randomized study of 150 patients undergoing abdominal surgery [3] sugammadex was compared to neostigmine in terms of residual paralysis incidence in the PACU. No patient had residual paralysis after reversal with sugammadex (0 out of 74) compared to 43% after neostigmine (33 out of 76) usual care patients. However, it should be emphasized that residual paralysis may still occur after reversal with sugammadex if a lower than recommended doseis administered [4].

Increasing worldwide use of sugammadex

Due to the above mentioned advantages over the "historical" anticholinesterase type antagonists, there is a reported increase in the use of sugammadex worldwide. A recent report from Perth, Australia [4], revealed that, sugammadex was introduced in 2011 and is currently used without access restriction. In 2013, 7000 doses of sugammadexwere given, representing a near complete shift to the rocuronium-sugammadex relaxant-antagonist combination. At Wolfson Medical Center in Israel, approximately 20% of cases are reversed with sugammadex. Of course, in many hospitals, the cost of sugammadex is an important limiting factor when contemplating the comprehensive replacement of neostigmine.

The same report from Australia [4] noted that the "one size fits all" dose of sugammadex may occasionally result in residual paralysis attributed to underdosing. Therefore, further staff education is necessary in this regard.

In December 2015, sugammadex was approved by the FDA (FDA News Release – 15 December, 2015).

Adverse effects, Contraindications & Precautions

Research regarding adverse effects, contraindications and precautions associated with sugammadex use is ongoing [5].

Among reported adverse effects, the most frequently encountered are bucking & movement in 3.0% of patients, dysgeusia (metal or bitter taste) & parosmia in 1%, bronchospasm in 2.6%, recurrent neuromuscular blockade related to suboptimal dose of sugammadex in 1.3%, and rarely allergic reactions [5]. The recent FDA report (FDA News Release – 15 December, 2015) also mentions as side-effects nausea/ vomiting, hypotension, pain, headache, temporarily reduction of the steroid contraceptives' effect and severe bradycardia responsive to atropine treatment.

There is not enough published data regarding the use of sugammadex in pregnant patients and in children younger than two years, although a few studies have shown successful off-label use of sugammadex in younger patients [6 –8]. No dose adjustment of the drug is necessary for elderly patients [5].

Torsadogenicity of sugammadex

Reversal of neuromuscular block with anticholinesterase–anticholinergic combinations has been associated with significant QTc prolongation, while such an effect has not been demonstrated for sugammadex, even at high doses [9].

Hypersensitivity associated with sugammadex administration

In a systematic review, including unpublished reports, Tsur and Kalansky [10] identified 15 cases of sugammadex hypersensitivity. Seventy three percent met World Anaphylaxis Organization criteria for anaphylaxis.

All cases occurred within 4-5 minutes subsequent to administration and it was concluded that awareness is required for the possibility of drug-induced hypersensitivity during the critical 5-minutes following sugammadex administration. The true incidence of sugammadex-induced hypersensitivity is not yet determined, though in view of the drug's extensive use, it appears to be a very rare event.

Sugammadex in the management of rocuronium-induced anaphylaxis

McDonnell [11] described a 33-yr-old female who suffered severe anaphylactic shock after rocuronium administration. After 19 minutes of ineffective traditional management, 500 mg sugammadex was administered with immediate haemodynamic improvement. The mechanism of this beneficial effect is unknown, however, in view of its own potential for causing anaphylaxis, a risk benefit ratio should be considered before treating rocuronium-induced anaphylaxis with sugammadex [12].

Use of sugammadex in patients with severe renal and/or hepatic impairment

Severe renal impairment (CrCl<30 mL/min) is a contraindication to sugammadex administration. The same is the case in patients with severe hepatic impairment, especially among patients with coagulopathy, though no studies in patients with severe hepatic failure have been reported [5]. Sugammadex, 4 mg/kg provided rapid reversal of deep rocuronium-induced block in renal and control patients. However, in renal failure patients, sugammadex-encapsulated rocuronium complex is detectable in plasma seven days after administration. High-flux haemodialysis is effective in removing the sugammadex-encapsulated rocuronium complexes [13].

Sugammadex and surgical bleeding

While sugammadex produced limited, transient (<1 hour) increases in activated partial thromboplastin time and prothrombin time, it was not associated with increased risk of bleeding compared to traditional care modalities [14].

Indications for the use of sugammadex

There are numerous clinical conditions where sugammadex reversal is reportedly preferred to reversal with an atropine-neostigmine combination. The list of indications is large and continually growing, as shown by published reports. The following is a list of clinical conditions in which sugammadex is preferentially used as reversal agent at Wolfson Medical Center:

- All bariatric surgery cases and morbidly obese patients undergoing other surgeries
- Unstable angina, tight aortic and tight mitral stenosis
- Residual paralysis after neostigmine reversal
- Myasthenia gravis and muscular dystrophies
- Patients with wasted muscle mass
- Pneumonectomies or other cases with severely limited lung reserves
- Failed intubation with difficult or failed ventilation after the administration of rocuronium, as we no longer use vecuronium and pancuronium

Other possible indications [15,16] are:

- operations terminated prematurely
- surgeries that require profound motor block for a short time (i.e. micro laryngeal surgery)
- other cases that require deep relaxation (i.e. laparoscopy) or whenever other reversal agents are contraindicated or ineffective.

The successful reversal of prolonged motor block after 15 mg total dose of rocuronium for caesarean delivery in a 70 kg patient treated with magnesium was first reported in 2012 [17]. At the end of surgery, 35 minutes after rocuronium administration, the patient had a TOF count and a PTC count of 0. Full motor recovery was re-established 60 seconds after the administration of 5.7 mg/kg sugammadex [17].

Use of rocuronium and sugammadex in morbidly obese patients

Small case series have shown that rocuronium for induction of anesthesia and sugammadex for reversal may be safe and effective in pregnant [18,19] and morbidly obese patients [20].

The elimination of rocuronium in morbidly obese patients may be delayed in those with fatty or fibrotic liver and reduced hepatic or renal blood flow.

There is some controversy about dosing of sugammadex in morbidly obese patients. Most authors recommend rocuronium dosing by ideal body weight and sugammadex dosing by IBW + 40% [21].

Following neostigmine reversal, the time from the appearance of T_2 in TOF count to TOFR 0.9 is much longer, 26 minutes in obese patients compared to 7 minutes in nonobese patients [22] and the "unsafe period of recovery", given as the time from visual loss of fade to TOF 0.9, is 0.3 minutes with sugammadex compared to 10 minutes with neostigmine [23]. Overall, sugammadex appears to be a safer and more predictable reversal agent in obese patients.

So far, the effect of reversal with sugammadex compared to neostigmine on postoperative respiratory complications has not been fully elucidated. In a retrospective study of 179 patients who had undergone laparoscopic sleeve gastrectomy, Ezri at al [24] have found no difference between the two groups in regard to the incidence of respiratory complications. Large, prospective, randomized trials are necessary to find the true advantage of sugammadex over neostigmine reversal

in decreasing the incidence of postoperative respiratory complications.

Rapid sequence induction (RSI) with rocuronium

While some authors consider that RSI with rocuronium is associated with fewer complications and better oxygenation during apnea, others report that succinylcholine provides better intubation conditions and shorter recovery time of failed intubation-failed ventilation scenarios [25-27]. These issues remain controversial and await further evidence.

In a randomized prospective study of 60 patients, Sørensen et al. [28] observed how rapidly spontaneous ventilation was re-established after RSI with either succinylcholine (1 mg/kg) or rocuronium (1 mg/kg) followed by 16 mg/kg sugammadex. Spontaneous ventilation returned 406 seconds after succinylcholine compared to 216 seconds after rocuronium-sugammadex. The time to T1 90% was 518 seconds with succinylcholine and 168 seconds with rocuronium-sugammadex. Conditions and time to intubation were not different between the two groups. The authors concluded that RSI with rocuronium-sugammadex combination allowed earlier spontaneous ventilation than with succinylcholine.

Rocuronium induction and difficult airway

Sørensen [28] has suggested that RSI with rocuronium is safe if sugammadex is readily available in case of failed airway management, even in patients with a difficult airway.

The induction with rocuronium in patients with predicted difficult airway may be too risky and sugammadex rescue reversal is recommended to be retained for use in unanticipated difficult airways [29]. When facing a failed intubation - failed ventilation scenario following rocuronium induction, practitioners need to have an appropriate dose of sugammadex immediately available. A "wake-up" decision has to be taken within a few minutes [29,30].

However, sugammadex administration does not guarantee return of spontaneous ventilation or easy mask ventilation and effective oxygenation, despite regaining motor strength. Other factors that may prevent effective oxygenation during recovery are airway oedema from repeated intubation attempts and mechanical airway closure due to laryngospasm or the presence of a foreign body.

The inappropriateness of using rocuronium in the case of a predicted difficult airway is demonstrated by several case reports where sugammadex was not helpful in obtaining effective oxygenation following failed intubation [31,32].

Therefore, we believe that whenever a difficult airway is suspected, "awake" fiber optic intubation may be a safer alternative to induction with rocuronium.

Use of sugammadex in the ICU and trauma patients

Gradually, sugammadex has been gaining popularity in intensive care (ICU) settings [33]. In ICU patients, sugammadex may be used in patients for whom succinylcholine is contraindicated, such as prolonged bedridden patients with disuse atrophy, burns, or major trauma. Other indications for sugammadex in the ICU include reversal of neuromuscular blockade given for short procedures where muscle relaxants are required or the treatment of residual neuromuscular blockade. The use of rocuronium for RSI in trauma patient, followed if necessary by sugammadex has been suggested by Ortega-Gonzalez [34].

Conclusions

Sugammadex is gaining popularity in the fields of anesthesia and intensive care. Devoid of the side effects of neostigmine and due to its ability to rapidly reverse even deep muscle relaxation, sugammadex seems to be superior to neostigmine as a reversal agent. Thus, it has the ability to save patients' lives following failed intubation – failed ventilation after rocuronium induction. However, elective rocuronium induction in patients with predicted difficult intubation is not recommended since sugammadex is not an absolute guarantee for a safe outcome in all failed intubation – failed ventilation scenarios.

Declaration of conflict of interest

Prof. Ezri has been invited speaker at scientific meetings in Israel, sponsored by MSD Pharmaceutical Company.

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