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**Sugammadex: Role in current anaesthetic practice and its safety benefits for patients**

Copp MV *et al.* Sugammadex in clinical practice

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**Abstract**

Sugammadex has revolutionized anaesthetic management of reversal of neuromuscular block (NMB) by way of its unique mechanism of action encapsulating the amino steroid neuromuscular blocking drugs rocuronium and vecuronium. The cholinesterase inhibitors have significant pharmacological and clinical limitations whereas sugammadex allows predictable, safe and rapid reversal from any depth of blockade. The financial cost of sugammadex is significant. Many hospitals in the United Kingdom use clinical guidelines to direct best use of sugammadex in their institutions. Auditing the use of sugammadex provides useful information on which patients are benefiting from sugammadex. The clinical benefits of sugammadex are well understood. No patient should now be subjected to the danger of post-operative residual curarization. Versatility in the ability to reverse neuromuscular block has brought opportunities to the anaesthetist in the management of rapid sequence induction using high dose rocuronium with the knowledge that safe reversal of NMB is now possible in the unlikely event of a “can’t intubate can’t ventilate” situation. Do we still need suxamethonium to be available? The nature of surgery continues to evolve with ever-increasing enthusiasm for minimally invasive laparoscopic techniques. There is evidence to support using a deeper level of NMB to improve the working space and operating conditions in laparoscopic surgery. It is now possible to maintain a deep level of NMB right up until the end of surgery with no concerns about the ability to effect safe reversal of NMB. Vigilance about the possibility of allergic sensitivity to sugammadex needs to be maintained. The increased usage of rocuronium has the potential for rocuronium-induced anaphylaxis. Conversely, there is a potential role for sugammadex in the treatment of rocuronium anaphylaxis. Clinicians who have used sugammadex are struck with the quality of recovery seen in their patients. It is important that the economic implications of the use of sugammadex are fully understood. This article considers the current role of sugammadex in clinical practice outside of routine reversal of NMB and discusses how the addition of sugammadex to the anaesthetic armamentarium brings safety benefits for patients.

**Key words:** Sugammadex; Neuromuscular block; Clinical benefits; Patient safety; Cost benefit

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**Core tip:** Sugammadex is a new drug to reverse neuromuscular blockade. Its unique mechanism of action has revolutionized the management of neuromuscular block. For the first time anaesthetists have the ability to reverse safely and predictably from any level of neuromuscular blockade transforming its clinical management. Post-operative residual curarisation can be eliminated bringing significant safety benefits to patients. Sugammadex is expensive and anaesthetists need to use it in a cost effective way for appropriate patients and anaesthetic techniques. Clinical guidelines can help in ensuring that sugammadex is used responsibly in current clinical practice.

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**INTRODUCTION**

Sugammadex was licensed for use by the European Medicines Agency on 29 July 2008 and launched for use in the United Kingdom in November 2008. It is now available for use throughout Europe, Asia, Japan, Australia and New Zealand. The anticipated launch of sugammadex in the United States has been put back after the Food and Drug Administration (FDA) cancelled its meeting in March 2015 of the Anesthetic and Analgesic Drug Products Advisory Committee, which was planned to discuss the resubmission of the New Drug Application for sugammadex.

MSD United Kingdom estimate that in the United Kingdom 70000 patients were given sugammadex last year and it is estimated that globally in excess of 8.9 million patients have been exposed to sugammadex without significant reported adverse events showing it to be a safe, effective and important new drug[1].

**CLINICAL ROLE OF SUGAMMADEX**

The original clinical trials evaluating sugammadex clearly demonstrate that it achieves faster and more predictable recovery of neuromuscular block from a moderate level of neuromuscular block as defined by a return of two twitches (T2) of the train of four (TOF) count and from a deep block of neuromuscular block at the level of a post tetanic count (PTC) of 1-2. The dose dependent response of sugammadex has also been shown to be effective in reversing safely from a profound level of block immediately after administration of an intubating dose of 1.2 mg/kg of rocuronium as used in a rapid sequence induction (RSI) of anaesthesia[2].

At the launch of sugammadex, emphasis was placed on the rapid and predictable reversal of neuromuscular block as compared to reversal with traditional cholinesterase inhibitors. The expectation was that sugammadex might universally replace the cholinesterase inhibitors in everyday clinical practice. The issue for the majority of clinicians and healthcare providers was the financial cost of sugammadex. In the United Kingdom such was the concern about the introduction of sugammadex on pharmacy and operating theatre budgets that many hospitals struggled to get formulary approval. In our own institution a guideline (Table 1) was written in an effort to inform usage in a rational manor to take advantage of the clear clinical benefits whilst trying to contain the likely adverse effect on the operating theatre budget[3].

We audited the use of sugammadex for the first six months after it became available. The aim of the audit was to check adherence to our guidelines and to give a quantitate figure for the overall use of sugammadex to inform effects on the operating theatre pharmacy budget.

In our institution approximately 18000 general anaesthetics are given per annum of which 15% use an NMB. In the first six months of sugammadex being available the drug budget for reversal agents (neostigmine + glycoplyrolate + sugammadex) increased by 60%. In the context of the total theatre pharmacy budget for our institution the overall increase in this budget was less than 1%. This is a reflection of the fact that conventional reversal (neostigmine + glycopyrrolate) is so inexpensive.

The clinical findings of the audit showed that 30% of cases where sugammadex was administered there was a desire to avoid the side effects of neostigmine, in particular the potentially detrimental effect of a tachycardia in patients with known ischaemic heart disease. Sugammadex was used in 28% of cases to help ensure complete reversal of NMB in morbidly obese patients undergoing non-bariatric surgery (at the time of the audit our institution did not have a Bariatric Surgery programme). Sixteen percent of cases were ear nose and throat cases where deep NMB was required right up until the end of surgery. Sixteen percent of cases involved a need to provide optimal surgical conditions with deep NMB up to the end of surgery during laparoscopic surgery. Five percent of cases were to reverse patients with a known difficult intubation in an attempt to avoid airway compromise from any element of residual neuromuscular block at extubation. Five percent of cases were ASA 3/4 patients undergoing emergency surgery where it was considered essential to avoid any potential element of residual block that would be likely to significantly compromise patients in the post anaesthesia care unit (PACU).

Most hospitals in the United Kingdom have subsequently used a guideline to help facilitate introduction of sugammadex into clinical practice. It is accepted that morbidly obese patients are at increased risk of postoperative anaesthesia related complications. In particular, morbidly obese patients undergoing non-bariatric surgery with a history of sleep apnoea are at risk of airway complications in the PACU. It is essential in this group of patients that the muscles of the upper airway, which are some of the most sensitive to the presence of a NMB and hence post-operative residual curarization (PORC), have achieved complete reversal at the time of extubation[4,5]. Sugammadex would seem to be ideally suited to reversal from NMB in this high-risk group of patients. Anaesthetists practising bariatric surgery are debating the use of a deep block technique compared to moderate block with remifentanil and further evidence is required to support the routine use of sugammadex in bariatric surgery.

There is clear evidence that critical respiratory events occur in the PACU as a result of PORC as shown by Murphy and colleagues[6]. In our institution we have recently published a case report of a patient who developed stridor in the PACU as a result of PORC which, when recognized as such, was swiftly and effectively resolved by sugammadex administration[7].

**RSI AND CAN’T INTUBATE CAN’T VENTILATE**

The traditional purist RSI using thiopentone and suxamethonium alone to induce anaesthesia and achieve endotracheal intubation is less commonly performed in UK clinical practice today. More often a modified form of RSI is carried out substituting thiopentone for propofol or supplementing the core induction medications with short acting opioids for dose sparing effect and in an attempt to obtund the laryngeal reflex during airway manipulation.

More recently, high dose rocuronium (1.2 mg/kg) has been shown to produce identical intubating conditions as suxamethonium[8]. Given the numerous side effects and contra-indications to suxamethonium this has become an increasingly attractive alternative. However, the use of rocuronium confers an intermediate duration of neuromuscular blockade (60-90 min)[9]. Prior to the introduction of sugammadex this would preclude the option of neuromuscular blocking agent reversal and waking a patient up in the event of a failed intubation, or indeed a Can’t Intubate Can’t Ventilate (CICV) scenario. However, with its potential to rapidly reverse a deep neuromuscular block, the question remains as to whether sugammadex has transformed the safety of a rocuronium based RSI.

Sugammadex reversal of profound neuromuscular block has been shown to be significantly faster than spontaneous recovery from suxamethonium[10]. Paton *et al*[11] reported on the successful use sugammadex after induction in a patient with airway difficulties. The key to a successful clinical outcome is early recognition of the CICV situation and administration of the appropriate dose of sugammadex (16 mg/kg) to reverse the intubating dose of rocuronium. It should be noted however, that the decision time to use sugammadex and its preparation in an emergency situation might cause significant delay in achieving full NMB reversal. Bisschops and Bisschops *et al*[12] (2010) demonstrated in simulation the extent of this delay and raise the concern that this may increase patient morbidity and mortality. If sugammadex is to be considered for CICV scenarios it must be readily available to be drawn up and immediately administered. In our trust we have put together an emergency reversal rescue pack stored in emergency theatres. It consists of three 500 mg ampoules of sugammadex, sufficient to recover a 93 kg patient that can be given promptly whilst exact doses are calculated and further sugammadex given as needed.

Individual experience must also be considered in the emergency use of sugammadex. Following its introduction, a number of hospitals in the United Kingdom only made sugammadex available in the theatre for the emergency treatment of a failed intubation. An individual poll conducted by the author at one such hospital found that no anaesthetist had actually ever used sugammadex. The concept that clinicians should use an unfamiliar drug in a difficult and potentially life-threatening situation could be questioned and may be criticised in the event of a poor clinical outcome. It follows that it could be considered unreasonable of an anaesthetist to use rocuronium for an RSI if they have no previous experience of using sugammadex in their own clinical practice.

Finally, we should perhaps be wary of becoming complacent with the availability of sugammadex in difficult airway trolleys. Mendonca warns of the risks of relying on sugammadex as a rescue plan in cases of anticipated difficult airway where awake tracheal intubation remains the gold standard[13]. The presence of sugammadex should not be a substitute for thorough pre-operative assessment of the airway, anticipation of difficulty and the presence of well thought out plans for management and back up.

**THE END OF SUXAMETHONIUM ?**

The arrival of sugammadex suggested that it would remove the need for suxamethonium[14]. Indeed the Difficult Airway Society guidelines are currently under review, due for publication in late 2015, and are likely to propose that rocuronium may be better than suxamethonium for RSI[15]. The question has been posed as to whether the availability of sugammadex will bring about the removal of suxamethonium from the anaesthetic drug cupboard. This issue was debated by Professor Mirakur RK and the author at the Annual Meeting of the British Association of Day Surgery[16]. It was agreed that whilst suxamethonium theoretically could be substituted by a rocuronium and sugammadex technique most clinicians feel uncomfortable not having access to suxamethonium, despite its considerable array of clinical side effects, in their clinical practice.

**DEEP NEUROMUSCULAR BLOCK (PTC 1-2)**

Sugammadex provides the anaesthetist for first time ever the ability to safely reverse from any level of neuromuscular block. This means that NMB could be maintained right up till the end of surgery without fear of having to prolong anaesthesia whilst waiting until the return of two twitches of the TOF to allow reversal with neostigmine and also fear of putting the patient at the potential risk of PORC.

Laparoscopic surgery is one area where the ability to maintain a deep level of block can bring safety benefits to the patient by improving intraoperative conditions for the surgeon. Over the last decade there has been a significant increase in the number and types of surgery that can be performed laparoscopically. The combined aims of the surgeon and anaesthetist are to do no harm, practice safe surgery, and produce an enhanced recovery for the patient. Major bowel surgery and the majority of gynaecological surgery are now routinely being performed using a laparoscopic technique. Avoiding large abdominal incisions brings real benefits to patients in terms of enhanced recovery.

The anaesthetist has a key role to play in assisting to provide optimal operating conditions for the surgeon right up until the end of surgery. There is evidence that provision of deep neuromuscular block can improve the operating conditions for surgeons, in particular the working space in laparoscopic surgery, with improved outcomes for patients[17,18]. In summary a deeper block prevents sudden unexpected patient movement, increases the working space, lowers intra-abdominal pressure (IAP) and may reduce postoperative pain[19-21].

However, the place for deep NMB in laparoscopic surgery has been questionedwith regard to the substantial economic considerations of maintaining deep block as compared to a less intensive block of TOF 1-3. Further evidence is required to ascertain if deep block contributes to better patient outcomes and truly improves surgical operating conditions[22].

**HYPERSENSITIVITY TO SUGAMMADEX**

One of the concerns consistently preventing approval of sugammadex by the United States FDA regards the potential risk of drug-induced hypersensitivity reactions. Case reports of anaphylaxis following sugammadex administration with confirmatory skin prick testing certainly exist in the literature[23,24]. A recent review article by Tsur and Kalansky[1] (2014) examined these reports in more depth. Of the 15 cases that they identified during a thorough search of the literature 11 underwent skin prick testing and 10 of these were proven to develop sugammadex induced hypersensitivity. Based on these cases they conclude that hypersensitivity reactions to sugammadex usually occur within 5 min of its administration with the appearance of a rash, hypotension and tachycardia being the most frequently shared signs. Of note, all of the patients during this review survived and in the majority of cases there had been no previous exposure to sugammadex. This raises the possibility that patients may have been previously sensitized by cyclodextrins found in food or cosmetics and that previous exposure to the drug itself is not a pre-requisite for hypersensitivity.

Despite the existence of reports of hypersensitivity, sugammadex use appears to be well tolerated and there remain no reports in the literature of deaths associated with its use[9]. Indeed, cyclodextrins are considered to be a relatively inert group of medicines and the doses of sugammadex used clinically are low in comparison to other medicinal products that contain these substances[9]. Current estimates of incidence of hypersensitivity reactions are less than 1%[25]. Ultimately, as with any medication that we administer, we should remain vigilant to the possibility of reaction and hypersensitivity and to have clear guidelines to manage such an event.

**SUGAMMADEX IN THE MANAGEMENT OF ROCURONIUM INDUCED ANAPHYLAXIS**

Conversely there has been some interest in the role of sugammadex in the management of rocuronium induced anaphylaxis. An allergic reaction to rocuronium is one of the most common causes of anaphylaxis in anaesthesia[9,26]. With the availability of sugammadex it is foreseeable that there will be an increase in the use of rocuronium as a muscle relaxant of choice. Consequently there may be a rise in the number of cases of rocuronium-induced anaphylaxis. If sugammadex has a role in the management of this potentially life-threatening emergency then its presence in the anaesthetic cupboards can be further justified.

Sugammadex binds rocuronium. Studies have demonstrated that once encapsulated, a rocuronium-sugammadex complex is formed and the epitope of the rocuronium molecule is concealed, preventing its role in facilitating further allergic reaction[27,28]. Current evidence in clinical practice remains at a case report level. Most of these describe an improvement in clinical condition following the administration of large doses of sugammadex immediately, or soon after the recognition of rocuronium induced anaphylaxis. Once an allergic process and mast cell activation have been triggered it is unlikely that encapsulation of the rocuronium will affect the anaphylactic cascade[9]. Despite this, there have been cases where sugammadex has appeared to improve clinical condition even 10 min after rocuronium anaphylaxis, which is more difficult to explain biochemically[29,30]. Of course, sugammadex is only one of a number of treatments given in attempt to attenuate the anaphylactic process and without further evidence it should not be considered a single therapy in itself, however, it’s role does appear to be expanding further than first thought.

**QUALITY OF RECOVERY**

Clinicians with wide clinical experience of sugammadex universally remark on the enhanced quality of recovery of their patients in the PACU who have had neuromuscular block reversed with sugammadex. It is difficult to objectively measure the “quality” of recovery from anaesthesia but why do patients who have been reversed with sugammadex subjectively seem to have a superior recovery?

One explanation put forward is the change in excretion of rocuronium. During spontaneous recovery, rocuronium is taken up by the liver and excreted in the bile with no metabolism. After sugammadex reversal, rocuronium will be excreted as a complex with sugammadex via the glomeruli in the kidney. As a result, the uptake mechanism in the liver does not have to deal with rocuronium. If another drug or drug metabolite is also removed via this liver uptake mechanism, the clearance of that drug will be improved. This hypothesis needs further evaluation. Alternatively, it could simply be that the rapid and complete restoration of muscle tone followed by activation of muscle spindles which results in activation of the arousal centre in the brain. One would expect to see changes in the EEG if this hypothesis was correct but this has yet to be clinically evaluated. After conventional reversal up to 70% of the NMJ receptors may still be occupied by NMB but still produce sufficient recovery of a TOF to 0.9 indicating a satisfactory clinical recovery[31]. When 100% of receptors are free of NMB following complete removal of rocuronium the increase in muscle tone and muscle spindle activity may contribute to the appearance of enhanced well-being and a better quality of recovery whilst patients are in the PACU.

**ECONOMIC CONSIDERATIONS AND COST BENEFIT**

In all healthcare environments the cost effective use of resources is paramount. The efficient use of the operating theatres and the PACU is an essential component of the cost effectiveness in any healthcare system. The debate that sugammadex brings economic efficiencies by increased case turnover in the operating room with reduced length of stay in the PACU will depend on the model of healthcare provision being utilized. It is clear that patients who are not fully recovered from neuromuscular block in the PACU have a delayed recovery room discharge[32].

There is an ever-increasing drive to improve theatre efficiency and facilitate rapid turnover between patients. Although “anaesthetic time” is often a relatively short part of the overall theatre time for each patient, certain operating lists can provide particular challenges for anaesthetists. Ear nose and throat and thoracic bronchoscopy surgery lists for example, where deep neuromuscular block is mandatory to enable surgical manipulation of the airway but with unpredictable, and often short, surgical time have traditionally proved difficult to manage efficiently for the anaesthetist. The side-effects of suxamethonium make it unattractive in these instances despite its rapid onset and offset, mivacurium remains unpredictable and other NMB require a certain timeframe before conventional cholinesterase reversal may be considered.

Short acting opioids such as alfentanil and remifentanil certainly have a role in facilitating such cases, however, they too confer side effects and alone may fail to achieve optimal surgical conditions. Sugammadex allows deep NMB with rocuronium that can then be completely reversed regardless of the duration of surgery. For this reason, in our Trust one of the agreed indications for sugammadex use is reversal from deep neuromuscular block that would otherwise waste 30 minutes of theatre time if waiting for a TOF count of 2 before administering neostigmine reversal (Table 1). The guideline relates to when a dose of rocuronium has been used to provide neuromuscular block for a surgical procedure where the surgery has finished earlier than predicted.

The clinical and cost effectiveness of sugammadex for the reversal of muscle relaxation after general anaesthesia in United Kingdom practice following routine and rapid induction of NMB was evaluated by Chambers and colleagues who concluded that sugammadex may be a cost-effective option compared with neostigmine+glycopyrrolate for reversal of moderate NMB[33]. There remain, however, considerable uncertainties about whether the full benefits of sugammadex can be realised in clinical practice.

The economic benefits of sugammadex depend upon the funding processes of the healthcare system within which it is being used. Paton *et al*[34] have suggested there may be some economic benefit to its use. The reality for most hospitals in the United Kingdom is that it has been a challenge getting sugammadex on to the hospital formulary. The difficulties are compounded depending on whether institutions take a macroeconomic view on budgets where it is accepted that in comparison to overall theatre costs, currently approximately 30 Euros/min, the costs of anaesthesia are small compared to the overall theatre costs. Some institutions take a micro economic view where drug costs are isolated, easy to calculate and more difficult to justify. Savings in theatre turnover time, increased productivity and reduced length of stay in recovery may well offset the cost of using sugammadex in individual cases. Certainly if the use of sugammadex helps avoid a clinical crisis with potential significant morbidity or to prevent an ICU admission then the use of sugammadex can be justified[35].

In practice we have not seen the universal uptake of sugammadex to replace cholinesterase inhibitors simply because the impact upon healthcare budgets would be prohibitive. Anaesthetists are generally cost conscious and although the cost of anaesthesia is small in relation to the resource utilized by our surgical colleagues the cost of drugs is easy to quantify and measure. This has meant that most anaesthetists will use sugammadex for selected cases only. In our own institution the guideline described exists to direct use of sugammadex, which is audited and reviewed on a regular basis.

**CONCLUSION**

The arrival of sugammadex presented the opportunity to change the practice of anaesthesia[36]. Sugammadex is a significant addition to the anaesthetic armamentarium enabling effective use of and safe recovery from the use of neuromuscular drugs when used as part of the classic anaesthesia triad of hypnosis, analgesia and muscle relaxation.

However, recognizing the reality of the cost implications of a blanket replacement of neostigmine+glycopyrrolate with sugammadex has lead clinicians to look carefully at how best to use this novel drug. Guidelines to direct use have helped to bring sugammadex onto hospital formularies.

The potential benefits of using sugammadex to avoid the well-known side effects of the conventional reversal agents in patients with significant clinical comorbidities are easily understood. The ability to provide a deep level of NMB for short periods of time without fear of an inability to reverse at the end of surgery is suited for certain surgical procedures. There is a belief that provision of a deeper level of block in particular for laparoscopic surgery has clinical benefits improving the operating conditions for surgeons and outcomes for patients but there needs to be further evidence to support this idea.

Sugammadex is a key rescue component of an RSI technique using high dose rocuronium in the rare scenario of a CICV where anaesthetists need to be familiar with its use. However, it would appear that we are not about to see suxamethonium disappear from the anaesthetic drug cupboard just yet. Finally, PORC in the recovery room although rare can be dealt with effectively in patients who have had a full dose of conventional reversal and the option of just waiting for the block to wear off consigned to history.

We suspect that the majority of anaesthetists in busy everyday clinical practice would welcome the chance to replace neostigmine universally with sugammadex but, with the ever-increasing pressure on healthcare budgets globally, this is highly unlikely to happen until sugammadex becomes more affordable.

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**Table 1 Suggested Guideline for use of sugammadex**

**Sugammadex is not to be prescribed for routine reversal from moderate NMB (TOF count > 2)**

1 Clinical situations where avoiding the use of neostigmine and glycopyrrolate potentially gives significant safety benefits to patients, *e.g.*, avoidance of tachycardia/tachyarrthymias in patients with ischaemic heart disease and/or atrial fibrillation. Avoidance of potential bronchospasm in patients with brittle asthma

2 Concern about residual neuromuscular block (after rocuronium or vecuronium) post-operatively in patients with airway difficulty or respiratory insufficiency that have already been reversed with a max 5 mg dose of neostigmine

3 Reversal from deep neuromuscular block that would otherwise waste 30 minutes of theatre time if waiting for a TOF count of 2 to use neostigmine reversal, *e.g.*, when a large dose of rocuronium has been used to provide deep neuromuscular block for a short surgical procedure or the surgery has finished earlier than predicted

4 In morbidly obese patients where there is a concern about the potential for residual neuromuscular blockade following reversal of NMB drugs

5 Emergency reversal of rocuronium (1.2 mg/kg) using the sugammadex rescue pack (16 mg/kg) after failed intubation at RSI

NMB: Neuromuscular block; TOF: Train of four; RSI: Rapid sequence induction.