Orthopaedic Surgery Implications Of A Novel Encapsulation Process That Improves Neuromuscular Blockade And Reversal

A Harris, M Welliver, R Redfern, N Kalynych, J McDonough

Abstract

Neuromuscular blocking agents have been used and developed over sixty years to facilitate surgical exposure and manipulation. Unfortunately, methods of terminating their paralytic effects have not, until recently, been improved upon. Currently approved neuromuscular blockade reversal options remain the same as they were over fifty years ago. These options allow metabolic and natural degradation or competitive antagonism. Competitive antagonism of neuromuscular blockade has significant limits and side effects. New pharmacology advances with the use of encapsulation to terminate the effects of neuromuscular blocking agents offers significant improvement over current reversal methodologies, with benefit to both patients and surgeons. Sugammadex, a selective relaxant binding agent, completely and reliably terminates steroidal neuromuscular blocking agents through the process of encapsulation and is therefore not associated with the adverse effects of traditional reversal agents. Application and implications for orthopaedic surgery is discussed.

INTRODUCTION

The terminology of "muscle relaxation" has remained in use for two main reasons. First, it is a much more pleasant phrase than "neuromuscular blockade" or "paralysis" when used in discussions with patients. The second reason is that it clearly describes what is currently provided. Often, muscle paresis, as opposed to muscle paralysis, is provided for surgeons. Only deep neuromuscular blockade will result in paralysis that provides total muscle laxity and this is often avoided during orthopedic procedures. This avoidance is due to the limitations and side effects associated with using neuromuscular blockade reversal agents and possibly a misunderstanding of the surgeon's needs. A review of current neuromuscular blockade methodologies and reversal limitations clarifies the current practice impediments to optimum muscular paralysis for surgical exposure and manipulation. The limitations and associated side effects of current neuromuscular blockade and reversal therapies reinforces the need for a new pharmacologic option that offers improved, reliable restoration of motor function after neuromuscular blockade.
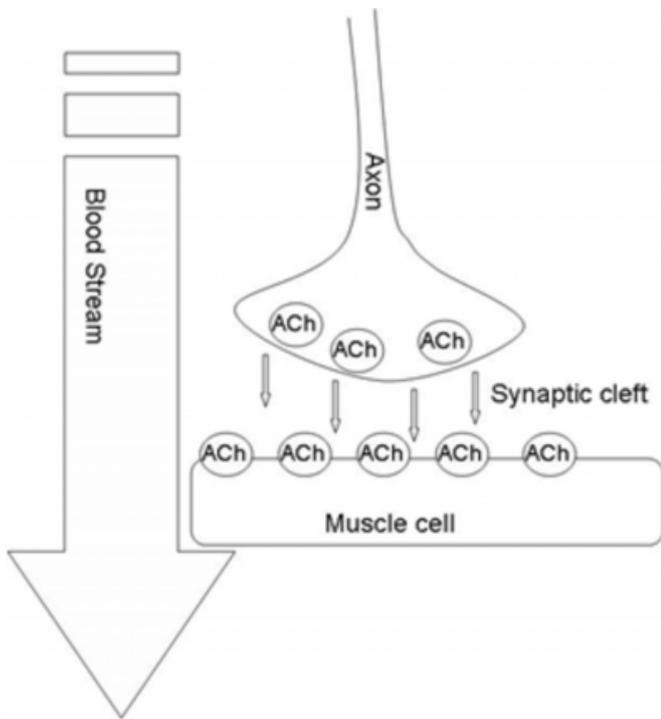
NEUROMUSCULAR BLOCKADE

RECEPTOR BLOCKADE

Normal motor function occurs from the release of the neurotransmitter acetylcholine (ACh) from synaptic vesicles in the nicotinic junction. Released ACh diffuses to ACh receptors located along the muscle fiber, and this chemical propagation of the neuronal impulse promotes muscle contraction.

Figure 1

Figure 1: Normal action of acetylcholine (ACh) at the nicotinic junction.

Pharmacologic induced paralysis occurs by neuromuscular blocking agent (NMBA) attachment to nicotinic ACh receptors at the neuromuscular cleft along the muscle cell. By occupying the receptors, NMBAs prevent ACh from binding to and stimulating these receptors.

Figure 2

Figure 2: Neuromuscular blocking agent (NMBA) occupying acetylcholine receptors.
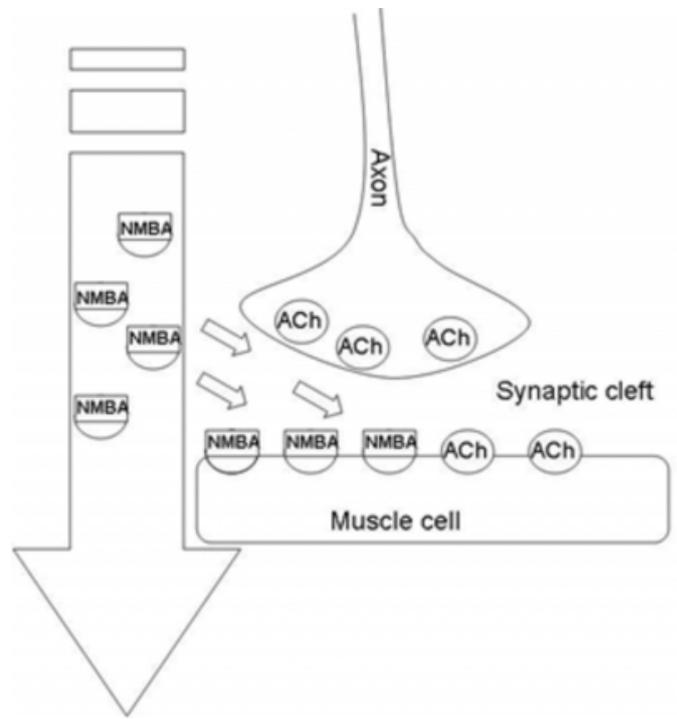

Motor neuron impulses are blocked from reaching the muscle fiber and muscular contraction is prevented. Varying levels of ACh receptor blockade provide varying levels of muscular relaxation. Only 100% receptor blockade completely prevents nerve impulses from reaching the muscle fibers. Deep neuromuscular blockade and resultant complete muscle paralysis requires high levels of NMBAs. Greater difficulty is encountered when attempting to reverse deep levels of neuromuscular blockade.

COMPETITIVE ANTAGONISM REVERSAL

The hesitancy to provide deep levels of neuromuscular blockade lie with the difficulties in reversing that blockade. Current reversal therapies use intravenously delivered cholinesterase inhibitors such as edrophonium (Tensilon®) and neostigmine (Prostigmin®) which increase the quantity of ACh molecules in the synaptic clefts of the nervous system. Increased quantities of ACh molecules are able to displace some NMBA molecules from their attachment on the ACh receptors and restore a level of motor function.

Figure 3

Figure 3: Cholinesterase reversal by increasing ACh and displacing NMBA from receptors.
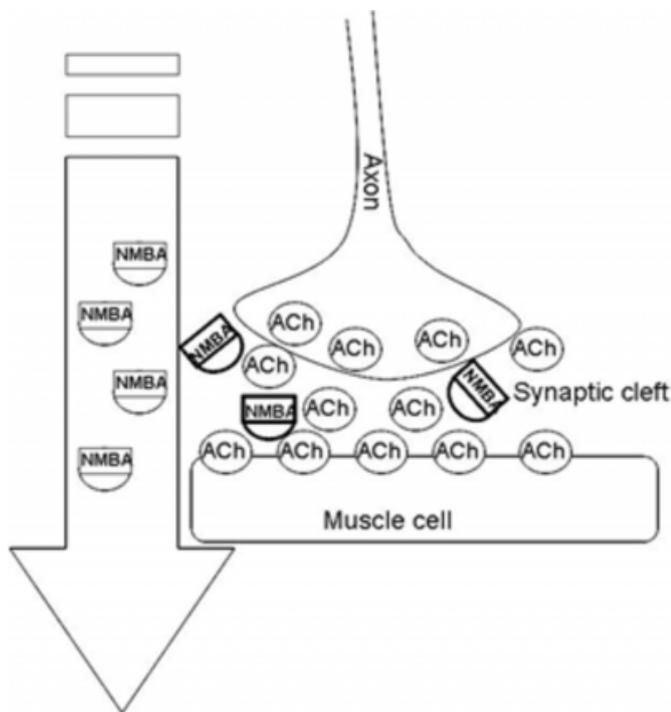
By competitively antagonizing the NMBA, motor impulses are able to reach the muscle fiber and muscular contraction is enabled. Complete displacement of NMBAs is not possible and as long as these molecules remain in the body they are able to maintain a degree of blockade despite "reversal". Recurarization (reattachment of displaced NMBA) and residual paralysis (undisplaced NMBA attached to the receptor), remain a primary clinical concern. Studies continue to show pulmonary compromise and delayed patient recovery times due to residual paralysis despite cholinesterase inhibitor reversal.[1,2,3,4] Current cholinesterase inhibitor reversal therefore is incomplete and limited in effectiveness especially with deeper levels of blockade.

The systemic increases of ACh from cholinesterase inhibitor reversal drugs also exert parasympathetic effects that are undesirable and potentially detrimental.[5] The parasympathetic effects include: bradycardia, bronchospasm, increased airway secretions, nausea, vomiting, abdominal cramping, and miosis. To counteract these side effects, anticholinergic drugs are given concomitantly. Anticholinergic drugs are effective in attenuating some of the cholinergic actions of reversal agents but also exert their own undesirable effects including: tachycardia, dry mouth, and mydriasis.[5,6] Hemodynamic variability associated with cholinesterase inhibitors and anticholinergics is well documented.[6,7] When current reversal drugs are viewed in light of their indirect action, limited ability to reverse deep levels of blockade, and side effects, the need for improvement is apparent. A pharmacologic improvement is emerging.

NOVEL ENCAPSULATION PHARMACOLOGY

Termination of neuromuscular blockade has been studied with a novel drug that encapsulates and binds neuromuscular blocking agents. Encapsulated termination of NMBAs has shown success in clinical study with the new drug, sugammadex, that offers complete and reliable return of motor function and a post operative course free of cholinesterase inhibitor and anti-cholinergic drug induced side effects and limitations.

CLINICAL STUDIES

Early experiments confirmed the high affinity of the experimental drug, Org 25969, now known as sugammadex, for the NMBAs rocuronium and vecuronium.[8, 9,10] Rocuronium and vecuronium are two widely used aminosteroid NMBAs of intermediate duration (30-60 min). Animal and clinical studies have consistently shown fast and effective reversal of these NMBAs.[10,11,12,13,14] Dose-response and safety studies have found a dose-dependent time to reversal of rocuronium and vecuronium-induced neuromuscular blockade with few side effects specifically associated with sugammadex.[11,13,14,15,16] Unintential overdosage of 2.5 times the recommended dosage of sugammadex was free of unwanted side effects.[17] Rex also concluded the safety and efficacy of deep neuromuscular blockade reversal with sugammadex.[18] Residual paralysis or re-paralysis after initial reversal was observed infrequently with sugammadex reversal and mainly with very low doses used in dose-finding studies[19]. To date, all clinical studies have concluded a dose-dependant, fast, safe, and effective reversal of rocuronium and vecuronium induced neuromuscular blockade.

SUGAMMADEX MECHANISM OF ACTION

Sugammadex is a modified cyclodextrin. Cyclodextrins are naturally occurring rings of glucose that geometrically resemble a truncated cone. The cavity created by the ring is lipophilic while the exterior is hydrophilic.[20] Cyclodextrins may encapsulate lipophilic drugs yet remain soluble in water. The natural cyclodextrins are composed of six, seven or eight glucose units called alpha, beta, and gamma
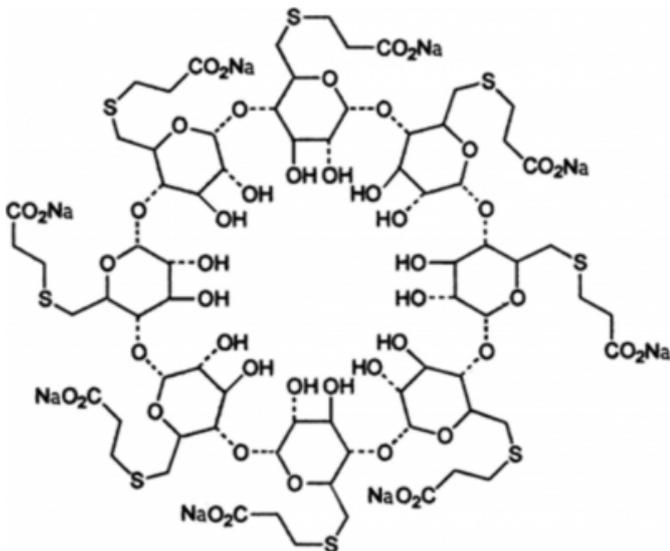
respectively.

Figure 4

Figure 4: The natural cyclodextrins.
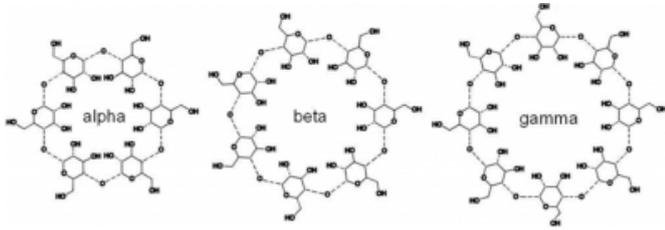
Sugammadex is synthesized from a gamma cyclodextrin modified with eight carboxyl thioether extensions added at the narrow rim.[8]

Figure 5

Figure 5: Sugammadex molecular structure.

This modification enlarged the cavity size increasing its affinity for two specific lipophilic NMBAs, rocuronium and vecuronium. In clinical studies published to date, interactions with other lipophilic drugs and endogenous steroids were not reported.[21,22] Further clinical and preclinical studies are expected to provide additional information. The ability of sugammadex to encapsulate and non-covalently bind rocuronium and vecuronium terminates their paralytic effects and effectively reverses their action. The mechanism of action is a one to one encapsulation of rocuronium or vecuronium molecules in the plasma.

Figure 6

Figure 6: Rocuronium molecule + sugammadex cyclodextrin = inclusion complex resulting in termination of neuromuscular blockade.
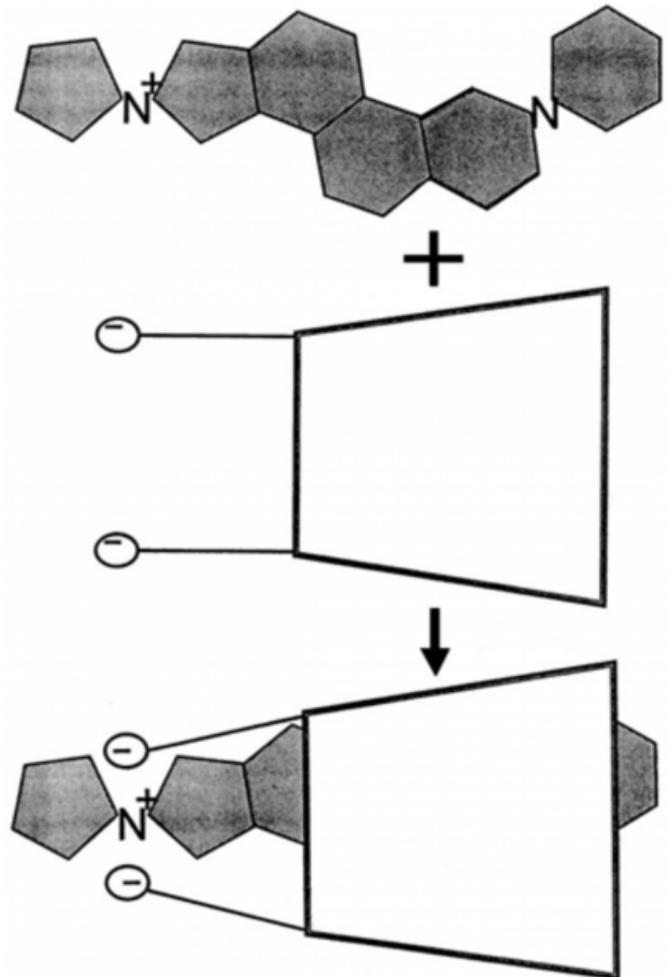
Once encapsulated, the NMBAs are no longer able to diffuse across tissue membranes to exert their action at the neuromuscular cleft. Any NMBA molecules present at the neuromuscular cleft exerting blocking effects are extracted off the receptors and back into the plasma by a reversed concentration gradient.

Figure 7

Figure 7: Sugammadex mode of action. Plasma encapsulation reverses concentration gradient and extracts NMBA molecules back into plasma for termination of neuromuscular blockade and restoration of normal motor function.
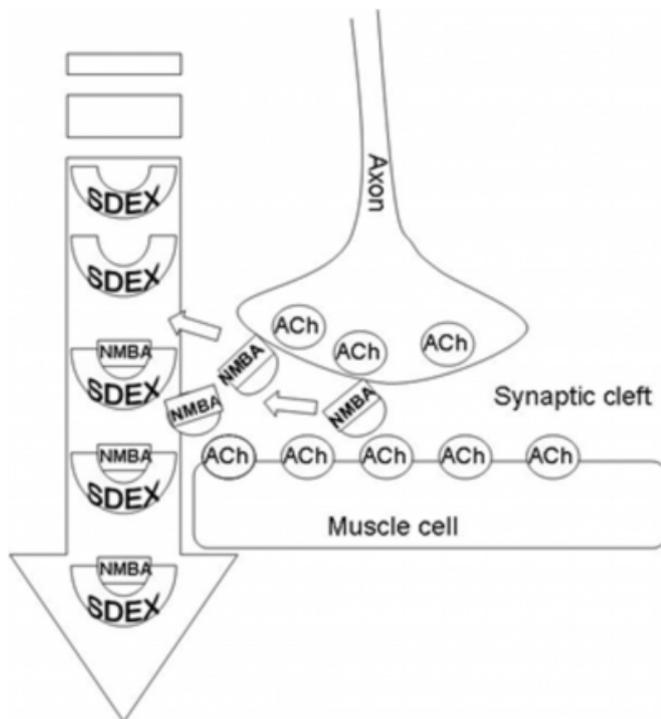
The NMBA molecules pulled into the plasma are quickly encapsulated with high affinity, preventing any further drug effect.[23] With adequate doses the reversal process occurs in its entirety within minutes. The resultant sugammadex bound NMBA (inclusion complex) is then excreted by the kidneys. Renal clearance of the NMBA has been found to be enhanced by sugammadex encapsulation.[15] An in-vitro study demonstrated that the inclusion complex was removed by dialysis.[24] This needs to be confirmed in clinical studies.

The perioperative benefits of a direct acting, complete, and reliable NMBA reversal drug are envisioned by both surgeons and anaesthetists. The improved ability to reverse NMBAs will enable the improved provision of neuromuscular blockade. Sugammadex is expected to allow greater depth of neuromuscular blockade and thus improve surgical exposure and manipulation by assuring full termination of blockade when desired.

DISCUSSION

Neuromuscular blockade is often required during orthopaedic procedures. A surgical procedure may start with adequate neuromuscular blockade but continual lessening block will make manipulations more difficult. Deep and continual neuromuscular blockade facilitates surgical exposures and manipulations and is preferred over partial (incomplete) blockade. Minimally invasive procedures with smaller incisions will benefit from deep blockade throughout the case including closure. Surgical times may be improved by removing the difficulties associated with muscular tension.

Fracture reduction unimpeded by muscular tension requires less force to bring the extremity out to length and allows for a more controlled reduction. This is extremely important for most diaphyseal fractures. The closed diaphyseal femur fracture reduced using traction with or without instruments is most easily performed by placing traction on the soft tissue envelope surrounding the fractured extremity to lengthen the fracture fragments. Muscular tone that restricts the ability to lengthen and manipulate the fracture increases the force required to realign and may risk additional injury to the patient. It has been concluded that the lack of adequate neuromuscular blockade was a likely factor for nerve injury during femoral nailing requiring traction.[25,26,27,28] The extensive traction required to counteract muscular tension during femur realignment contributed to longitudinal nerve tension and direct compression on the perineal post of the fracture table. [25,26,27,28] This direct nerve compression and stretching has resulted in post operative erectile dysfunction. Lower incidence of nerve injury in patients who received greater doses of NMBAs upholds the authors' recommendation for "optimal muscle relaxation during fracture reduction"[26] It has been suggested that deeper neuromuscular blockade may have prevented the negative outcome and cautioned others to be aware of this risk.[26,27]

The novel pharmacologic action of sugammadex provides faster reversal of NMBAs free of cholinesterase inhibitor limitations and side effects, and promises benefit beyond allowing deeper neuromuscular blockade with effective recovery. Sugammadex will likely shorten, time to extubation, patient recovery and time to discharge. Orthopaedic trauma patients requiring immediate surgery will benefit from expanded NMBA choices to rapidly secure the airway. Currently, only succinylcholine, a depolarizing short acting muscle relaxant with a high degree of side effects, allows anaesthetists to quickly control the airway and intubate the trachea without the risk of extended paralysis should ventilation or intubation become difficult. Rocuronium, a non-depolarizing NMBA, at doses of 1.2

mg/kg and higher allows quick onset and rapid-sequence intubation ability with minimal side effects.[29] Prior reluctance to use rocuronium is due to its extended duration of neuromuscular blockade. Sugammadex is expected to provide the ability to rapidly terminate rocuronium-induced paralysis, and restore motor function and spontaneous ventilation should intubation fail.[27] Sugammadex termination of rocuronium's effects is faster than succinylcholine degradation by plasma enzymes (at the appropriate dose) and may provide another option for rapid sequence intubations.[14,30]

Additionally, the adverse effects of residual paralysis in postoperative patients, which is commonplace with conventional cholinesterease inhibitor reversal, may be avoided with sugammadex encapsulation reversal.[31] Residual paralysis impairments of respiratory function that promote airway obstruction, hypoxemia, and atelectasis are eliminated with complete reversal.[32] Sugammadex rescue of residual paralysis due to incomplete reversal by conventional reversal drugs has been accomplished by Lenz to relieve respiratory distress.[33] The differential diagnosis of low level residual paralysis versus other compromising factors may also be achieved by delivery of sugammadex when respiratory compromise is not definitively known but suspected to be incomplete reversal by cholinesterase inhibitors.

CONCLUSION

Continual study has and may continue to uncover improved patient outcomes using the modified cyclodextrin, sugammadex. Large scale use of sugammadex after FDA approval will ultimately determine the full benefits derived from this new reversal agent. Despite few significant adverse events associated with this drug in clinical studies to date, only large patient populations receiving this drug and thorough phase will conclusively determine its full safety and efficacy.

It is clear however, that deep neuromuscular blockade (complete laxity) facilitates easier reductions and potentially will decrease traction related complications. The pharmacologic assurance of NMBA reversibility no longer warrants less than profound neuromuscular blockade when required. Complete control of terminating NMBA induced paralysis will promote optimal surgical conditions by allowing deeper levels of neuromuscular blockade during cases. The understanding of the new NMBA reversal

pharmacology of sugammadex coupled with communication between surgeon and anaesthetist will foster one of the paradigm shifts that marks the future of orthopedic surgery.[34]

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