

GOOD BYE SUXAMETHONIUM

Prof.Dr.I.Chandrasekaran.MD.,DA.,

PROF & HOD.,INSTITUTE OF ANAESTHESIOLOGY,

GOVT., RAJAJI HOSPITAL AND MADURAI MEDICAL COLLEGE,

MADURAI.

INTRODUCTION:

Neuro muscular blockers (NMB) are required to facilitate intubation, to provide muscle relaxation for surgery, to enable positive pressure ventilation and to restrain the patient from movement during surgery.

The ideal characteristics of a neuromuscular blocker that facilitates intubation are rapid onset profound relaxation, short duration of action and complete recovery from paralysis after intubation, without any side effects. These characteristics are specially important when the neuro muscular blocker must be used as a component of Rapid Sequence Induction and tracheal intubation in emergency situations

Since its introduction in 1949, suxamethonium has enjoyed its long tenure as the fastest and shortest acting muscle relaxant. It is the only depolarising muscle relaxant in clinical use at present. Though it meets the ideal characteristics, it is not without side effects.

Suxamethonium has numerous unwanted side effects:

Muscle pain. Occurs commonly, especially in young, fit adults with early ambulation. Strategies such as precurarization exist to reduce the incidence but no strategy is fully preventative.

Bradycardia. Occurs due to stimulation of muscarinic receptors in the sino-atrial node. Bradycardia is more common in children and after repeated doses of the drug. It is due to succinyl monocholine.

HYPERKALEMIA: This is due to release of potassium from muscles during depolarising block. In normal healthy individuals, the rise in Potassium is in the range of 0.5 MEq/L which is well tolerated. This normal rise may not be tolerated by patients with renal failure and pre-existing hyperkalemia. The release may be massive in patients with burns, prolonged immobilisation, patients with cerebrovascular accidents and paralysis which can induce bradycardia and cardiac arrest.

Increased intra-ocular pressure. There is a theoretical risk of expulsion of vitreal contents with the use of suxamethonium in patients with a penetrating eye injury.

Increased intragastric pressure. Fasciculations induced by suxamethonium increase the intragastric pressure and can predispose to regurgitation and aspiration of gastric contents

Phase II block. This may occur after large or repeated doses of suxamethonium. Neuromuscular block is prolonged and peripheral nerve stimulation results in fade of the train-of-four twitch height response and post tetanic facilitation..

Prolonged block due to reduced plasma cholinesterase activity. This may be due to congenital or acquired causes. Acquired causes include reduced enzyme synthesis, which may occur in liver disease, carcinomatosis, pregnancy or starvation (hypoproteinaemic states), cardiac failure, renal failure, and burns. The co-administration of other drugs such as etomidate, ester local anaesthetics, methotrexate, remifentanyl and esmolol can result in a reduction in plasma cholinesterase activity.

Inherited causes of prolonged block after suxamethonium occur due to production of atypical plasma cholinesterase. The structure of the cholinesterase enzyme is determined genetically by a gene on chromosome 3. Three variants from the usual gene exist and are known as the atypical, silent and fluoride resistant genes. Individuals with these variant genes have atypical cholinesterase enzyme, and have a prolonged neuromuscular block after suxamethonium. Duration of prolonged block varies from 30 minutes (eg. People heterozygous for the atypical gene) to several hours (eg. homozygotes for the silent gene.)

Malignant hyperthermia. This condition may be triggered by suxamethonium and therefore its use is absolutely contraindicated in susceptible patients.

Anaphylaxis. Suxamethonium is responsible for over 50% of anaphylactic reactions to NMBDs

Why do we need a replacement?

Whenever a drug is introduced into clinical practice, apart from its uses, its side effects become evident because of its use in a huge and varied population of patients. Simultaneously, research starts to avert these side effects or into the invention of yet another new or next generation of drug with better effects and fewer side effects.

Anaesthetic drugs are no exceptions.

ETHER, CHLOROFORM, TRICHLOROETHYLENE, CYCLOPROPANE, TUBOCURARINE, GALLAMINE, HALOTHANE, ENFLURANE . THESE ARE SOME DRUGS WE HAVE THOUGHT TO BE "GOLD STANDARDS" AND IRREPLACEABLES

BUT RESEARCH AND DEVELOPEMENTS HAVE REPLACED THESE DRUGS OUT OF OUR ARMEMENTARIUM AND GIVEN US SAFER AND BETTER DRUG

RAPACURONIUM

Rapacuronium was the first non-depolarizing neuromuscular blocker introduced in 1999 which is rapidly acting, short duration of action made possible by reversal with neostigmine in clinical anaesthesia .

Due to risk of fatal bronchospasm it was withdrawn from the United States market by Organon on March 27, 2001

ROCURONIUM: FAST ONSET

Introduced in 1994, Rocuronium is an aminosteroidal derived non-depolarizing neuromuscular blocking agent with a rapid to intermediate onset depending on dose, that also has an intermediate duration of action. Rocuronium is used to facilitate endotracheal intubation, to provide skeletal muscle relaxation during surgery, or facilitate mechanical ventilation in intubated, critically ill patients.

Rocuronium is a low potency neuromuscular blocker. Hence the larger dose used for inducing paralysis acts fast. This is called MOLAR POTENCY

Though introduced in 1994, reversal from the effect of Rocuronium depended on neostigmine which could not be performed till spontaneous recovery started.

Research into newer reversal agents identified Cyclodextrins as potential agents. From then, Gamma Cyclodextrin, the reversal agent specific for rocuronium was engineered. The main advantage of this drug is that it has cholinesterase independent action and reversal can be contemplated whenever needed without the fear of incomplete recovery or delayed re paralysis

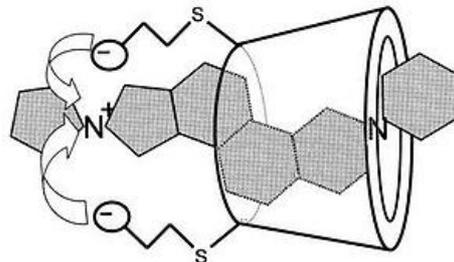
Rocuronium in a dose of 0.6 mg/kg produces good intubation condition in 90 seconds and a dose of 0.9mg/kg produces good intubation condition within 60.0 seconds, comparable to that of suxamethonium, without any side effects.

The main advantage of rocuronium is its safe cardiovascular profile, no histamine release and its rapid reversal enabled by the presence of sugammadex.

SUGAMMADEX: INDUCING FAST RECOVERY

(Su refers to **s**ugar and **gammadex** refers to the structural molecule **γ**-cyclodextrin)

The structure of cyclodextrin has a hydrophobic cavity and a hydrophilic exterior because of the presence of polar hydroxyl groups.



Hydrophobic interactions of a drug into the Cyclodextrin cavity results in the formation of a water-soluble guest(drug) – host (cyclodextrin) complex. For this reason, cyclodextrins have been used as solubilizing agents for many United States Food and Drug Administration-approved drugs, and have been evaluated as solvents for different anesthetic drugs such as propofol, midazolam, bupivacaine, and sufentanil

This gamma cyclodextrin has been modified from its natural state by placing eight carboxyl thio ether groups at the sixth carbon positions. These extensions extend the cavity size allowing greater encapsulation of the rocuronium molecule.

Sugammadex exerts its effect by forming very tight complexes at a 1:1 ratio with steroidal neuromuscular blocking drugs (rocuronium > vecuronium > pancuronium). The guest–host complex exists in equilibrium with a very high association rate (an association constant of 10^7 M^{-1}) and a very low dissociation rate, so the complex is tight

Sugammadex's binding encapsulation of rocuronium is one of the strongest among cyclodextrins and their guest molecules. The rocuronium molecule (a modified steroid) bound within sugammadex's lipophilic core, is rendered unavailable to bind to the acetylcholine receptor at the neuromuscular junction.

During rocuronium-induced neuromuscular blockade, the IV administration of sugammadex results in rapid removal of free rocuronium molecules from the plasma. This creates a concentration gradient favoring the movement of the remaining rocuronium molecules from the neuromuscular junction back into the plasma, where they are encapsulated by free sugammadex molecules. The latter molecules also enter the tissues and form a complex with rocuronium. Therefore, the neuromuscular blockade of rocuronium is terminated rapidly by the diffusion of rocuronium away from the neuromuscular junction back into the plasma.

The main advantage of sugammadex is reversal of neuromuscular blockade without relying on inhibition of acetylcholinesterase. Therefore it does not cause the autonomic instability produced by anticholinesterases such as neostigmine, and antimuscarinic agents such as atropine do not need to be co-administered.

A change in acid–base status affects anticholinesterase activity, it appears not to influence the efficacy of sugammadex

The compound's efficacy as an antagonist does not appear to rely on renal excretion of the cyclodextrin-relaxant complex. Most sugammadex is excreted unchanged in the urine in the first 8 h. Sugammadex also increases the amount of rocuronium excreted unchanged in the urine.

Sugammadex is ineffective against succinylcholine and benzylisoquinolinium neuromuscular blockers, such as mivacurium, atracurium, and cisatracurium, because it cannot form inclusion complexes with these drugs. Therefore, if neuromuscular blockade must be re-established after using sugammadex, succinylcholine or one of the benzylisoquinolinium neuromuscular blockers should be considered.

The interaction of sugammadex with other molecules has been tested with isothermal titration microcalorimetry. The ability of sugammadex to form complexes with other steroidal and nonsteroidal compounds, such as cortisone, atropine, and verapamil, is probably clinically insignificant and is approximately 120–700 times less than that of rocuronium. The high affinity of sugammadex for rocuronium and vecuronium is caused by the interaction between the negatively charged carboxyethyl side chains of sugammadex and the positively charged quaternary nitrogen of rocuronium and vecuronium. As endogenous steroidal hormones and steroidal drugs lack the quaternary nitrogen of the steroidal blockers, they show a much lower affinity. Furthermore, steroidal hormones are also bound tightly to specific protein carriers; for example, the sex hormones are bound with very high affinity to globulin.

DOSE OF SUGAMMADEX

The effectiveness of sugammadex is dose dependent.

The administration of 8 mg/kg sugammadex 3 min after the administration of 0.6 mg/kg rocuronium resulted in the recovery of the TOF ratio to 0.9 within 2 min. Decreasing the dose of sugammadex to 4 mg/kg resulted in a recovery of the TOF ratio to 0.9 in <4 min.

Doses of 2.0–4.0 mg/kg of sugammadex reversed rocuronium-induced neuromuscular blockade within 3 min.

Unexpectedly, the recovery time was longer (2.6 min [range 1.3–3.9 min]) with a 6.0 mg/kg dose. The reason for this deviation is unclear, but the reversal still occurred in <3 min, on average.

HIGH DOSE ROCURONIUM BLOCK REVERSAL | Currently, as a part of a multicenter study, we are comparing the speed of recovery from 1.2 mg/kg rocuronium followed 3 min later by 16 mg/kg sugammadex with that of spontaneous recovery from 1.0 mg/kg succinylcholine in surgical patients. Our initial results are very encouraging with respect to the antagonism of this profound level of rocuronium-induced neuromuscular blockade and indicate that the total duration from administration of rocuronium until a TOF ratio recovery to more than 0.9 is shorter than the time needed for spontaneous recovery from 1.0 mg/kg succinylcholine-induced blockade to a similar degree of recovery.

SIDE EFFECTS

Sugammadex is biologically inactive, does not bind to plasma proteins, and appears to be safe and well tolerated. The safety of sugammadex has been assessed in the phase I and II studies (in a total of 86 subjects). In one study, sugammadex was administered to awake volunteers who had received no neuromuscular blocking drugs. The most frequently reported side effects have been hypotension (three subjects), coughing (three subjects), movement (three subjects), nausea (three subjects), vomiting (three subjects), dry mouth (four subjects), parosmia (an abnormal smell) (two subjects), a sensation of a changed temperature (three subjects), and abnormal levels of *N*-acetyl-glucosaminidase in the urine (five subjects). In one study, prolongation of the corrected QT interval was noted in five subjects who received placebo and in three subjects who received sugammadex.

WILL IT REPLACE SUXAMETHONIUM

Why would one ever give succinylcholine if one could give rocuronium and achieve reversal more quickly than the succinylcholine would wear off? Before these questions can be answered, however, we must know whether the rocuronium-sugammadex sequence will be safer than succinylcholine? In this regard, studies using succinylcholine have indicated that the risk of desaturation in the immediate postinduction period is much greater than initially recognized in “cannot intubate, cannot ventilate” situations.

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The introduction of propofol almost two decades ago changed anesthetic practice. Nothing since then, however, has had the same effect. Unquestionably, the introduction of sugammadex is an important breakthrough, and one that is likely to change the face of clinical neuromuscular pharmacology. This molecule is specifically suited to rocuronium and vecuronium, and its future clinical use should decrease the incidence of postoperative muscle weakness caused by these drugs and facilitate the use of rocuronium for rapid sequence induction of anesthesia.

For now, however, we still need benzylisoquinolinium neuromuscular blockers in our practice, so the residual postoperative muscle weakness caused by this class of drugs is likely to continue unless objective neuromuscular function monitors are routinely used, or until a molecule capable of binding to benzylisoquinolinium neuromuscular blockers is discovered.

NEWER DRUG UNDER RESEARCH:

GANTACURIUM:

Gantacurium chloride (formerly recognized as GW280430A and as AV430A) is a new experimental neuromuscular blocking drug or skeletal muscle relaxant in the category of non-depolarizing neuromuscular-blocking drugs, used adjunctively in surgical anesthesia to facilitate endotracheal intubation and to provide skeletal muscle relaxation during surgery or mechanical ventilation. Gantacurium is not yet available for widespread clinical use: it is currently undergoing Phase III clinical development

. The singular distinguishing clinical feature of gantacurium from any other non-depolarizing neuromuscular blocking drug clinically tested is that it has the desired duality of a rapid onset and an ultrashort duration of action even when administered at 3-4 times the ED₉₅ doses. With the exception of one other clinically tested agent, BW785U77, no other clinically administered neuromuscular blocking drug has matched this feat to date: all other non-depolarizing neuromuscular blocking drugs clinically administered at equivalent doses most certainly would result in a medium or long duration of action albeit with a rapid onset of paralyzing effect. In this sense, gantacurium is a first in its class non-depolarizing neuromuscular blocking drug to arguably challenge the pharmacological profile of the gold-standard ultrashort acting depolarizing agent succinylcholine.

BW785U77 was not pursued for further clinical development owing to its propensity for eliciting histamine release in humans with more intensity than that observed during pre-clinical evaluation in animals.

Preliminary *in vitro* investigations indicate that the *in vivo* pharmacological activity likely undergoes rapid "chemo-inactivation" via cysteine adduct formation followed by slow biodegradation via ester hydrolysis. The pharmacologically inert cysteine adduct subsequently undergoes ester hydrolysis and the by-products are eliminated via renal and/or hepatic mechanisms. Unlike the pH- and temperature-dependent chemodegradation seen with atracurium and cisatracurium, the inactivation of gantacurium via cysteine adduct formation is independent of body pH and temperature.

The use of extrinsically administered cysteine to deliberately accelerate reversal of the pharmacological effect of fumarate *bis*-onium neuromuscular blocking drugs is being investigated currently.

CONCLUSION:

“Necessity is the mother of inventions”. Changing anaesthetic practises, improved patient safety have necessitated the discovery of newer and better drugs. Since the introduction and clinical use of ether, research has brought in better and safer drugs into anaesthetic practise.

Suxamethonium is a drug that had many ideal characteristics necessary for rapid induction of muscle relaxation to facilitate laryngoscopy and intubation, and a rapid wear off, facilitating a prompt and complete recovery. This was particularly useful in rapid sequence intubation and intubating patients with a predicted difficult airway where a patient will recover if a “cant intubate cant ventilate” situation arises. But suxamethonium is not without side effects. Hyperkalemia, increased intragastric pressure, bradycardia, have limited its use in patients and has caused serious problems. The fear aspiration during rapid sequence induction and fear of cant intubate cant ventilate situation in patients with difficult airways has made us use suxamethonium despite its side effects.

Though Rocuronium was introduced in 1994, and had a very fast onset of action, it could not be used in patients with difficult airway since it has an intermediate duration of action. Research into chelating agents for rocuronium led to the discovery of Sugammadex which has helped us overcome the only problem in rocuronium, i.e., intermediate duration of action.

With Sugammadex it is now possible to achieve rapid onset and fast recovery from neuromuscular block. Sugammadex reversal at the end of surgery also avoids the complications of anticholinesterase drugs like neostigmine.

Rocuronium Sugammadex combination is promising us a safer future in anaesthesia. And the days to say goodbye to suxamethonium are not far off.

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