Introduction

Adequate reversal of neuromuscular block is an important consideration in anaesthesia. Restoration of normal neuromuscular function may occur spontaneously or may be hastened with the use of acetylcholinesterase inhibitors such as neostigmine ***(Shieds et al., 2006)***.

Acetylcholinesterase inhibitors, however, have some problems as incomplete reversal or residual block in the recovery room, and a relatively high incidence of cholinergic side effects, as bradycardia, hypotension, bronchoconstriction, vomiting etc. They are effective in reversing neuromuscular block (NMB) only if given when partial recovery of NMB is reached due to its indirect action. Muscarinic antagonists such as atropine when administered concomitantly may result in tachycardia, dry mouth and mydriasis ***(Naguib and Lien, 2005).***

On review of current neuromuscular reversal drugs, their indirect action, limited ability to reverse deep levels of blockade and side effects, highlight the need for improvement. Sugammadex *(ORG 25969)* - the novel selective relaxant binding agent may fit the bill ***(Tayal et al., 2008).***

Sugammadex is a modified γ-cyclodextrin which is cyclic oligosaccharide carbohydrates. They have a ring structure with a hydrophobic surface that allows cyclodextrins to dissolve in water, as well as to form complex hydrophobic molecules within the central core ***(Naguib, 2007).***

Sugammadex exerts its action by forming very tight complexes in 1:1 ratio with steroidal neuromuscular blocking drugs and functions as an irreversible chelating agent. Hydrophobic interactions trap the drug into the cyclodextrin cavity (the doughnut hole), resulting in the formation of a water-soluble guest-host complex known as chemical encapsulation or chelation ***(Shields et al., 2006).***

Sugammadex has no effect on acetylcholinesterase. This eliminates the need for anticholinergic drugs, thus avoiding their undesirable side effects ***(de Boer et al., 2006).***

Many studies have examined a dose-response relationship with sugammadex for reversal of neuromuscular blockade. However, still literatures are deficient in comparing efficacy of sugammadex in reversal of deep block of rocuronium and pancuronium.

Aim of the Study

Neostigmine is commonly used as reversal of neuromuscular blockade, however, it may cause hypotension, bradycardia, bronchoconstriction and vomiting which may be deleterious in some patients or even may be contraindicated.

The aim of this study is to assess the efficacy of sugammadex in reversal of deep neuromuscular blockade induced by steroidal muscle relaxant in surgical patients. We will use rocuronium & pancuronium. In addition, safety variables (particularly adverse event information) of sugammadex will be assessed.

Chapter (1)

Pharmacology of Sugammadex

Muscle relaxants are routinely used worldwide as part of a modern concept of balanced anaesthesia. They can be categorized as depolarizing (e.g., succinylcholine) and nondepolarizing (steroid-based and benzylisoquinoline) muscle relaxants. Although nondepolarizing muscle relaxants have very few adverse effects (mostly allergic reactions) during anaesthesia, a residual duration of action of muscle relaxants beyond the end of the operation, also referred to as postoperative residual curarization, is a well-known problem. Postoperative residual curarization can lead to respiratory insufficiency, impaired upper airway function, and increased risk of aspiration and consequently, of the risk of postoperative pulmonary complications ***(Murphy et al., 2008).***

For decades, anaesthesiologists have had three options for avoiding postoperative residual curarization and its complications:

1. They can opt not to use muscle relaxants at all. This, however, is not considered state of the art practice for several reasons: endotracheal intubation without using

muscle relaxants increases the possibility of a difficult intubation, the risk of iatrogenic laryngeal trauma, and postoperative hoarseness ***(Combes et al., 2007).***

2. They can wait until the muscle relaxant is metabolized and neuromuscular transmission and muscle function has fully recovered spontaneously. However, aside from the different durations of action of the different muscle relaxants, there are also enormous inter individual differences in the speed that muscle relaxants are metabolized and therefore, in how fast the patient recovers from paralysis ***(Debaene et al., 2003).***

3. They can antagonize the residual effect of muscle relaxants with a cholinesterase inhibitor, e.g., neostigmine. This antagonism, however, has shortcomings:

    a. Cholinesterase inhibitors work indirectly by increasing the acetylcholine concentration in the neuromuscular junction. This increases the chance of displacing the muscle relaxant from the acetylcholine receptor. Cholinesterase inhibitors can therefore only be used if the neuromuscular function has already recovered to a certain degree. In general, sufficient

recovery to enable antagonism reversal is beyond a train of four (TOF) count of 4.

b. As cholinesterase inhibitors act, not only at the neuromuscular junction, but also, in the parasympathetic system, they have numerous unwanted side effects, e.g., bradycardia. Thus, they are typically combined with a muscarinic antagonist (para sympatholytic drug), such as glycopyrrolate or atropine.

c. With the invention of sugammadex, a completely new possibility of neuromuscular block reversal was introduced to anaesthesia practice ***(Murphy et al., 2008).***

Molecular characteristics:

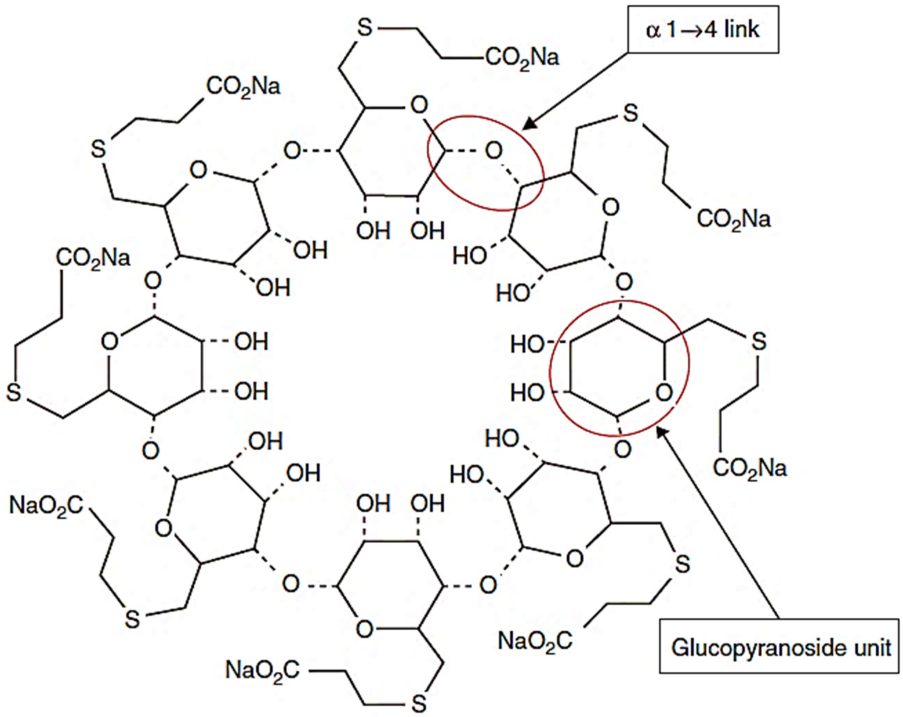

Figure (1): Structure of sugammadex showing eight glucopyranoside units linked together via a 1 → 4 linkages to maintain a doughnut-like shape ***(Welliver, 2007).***

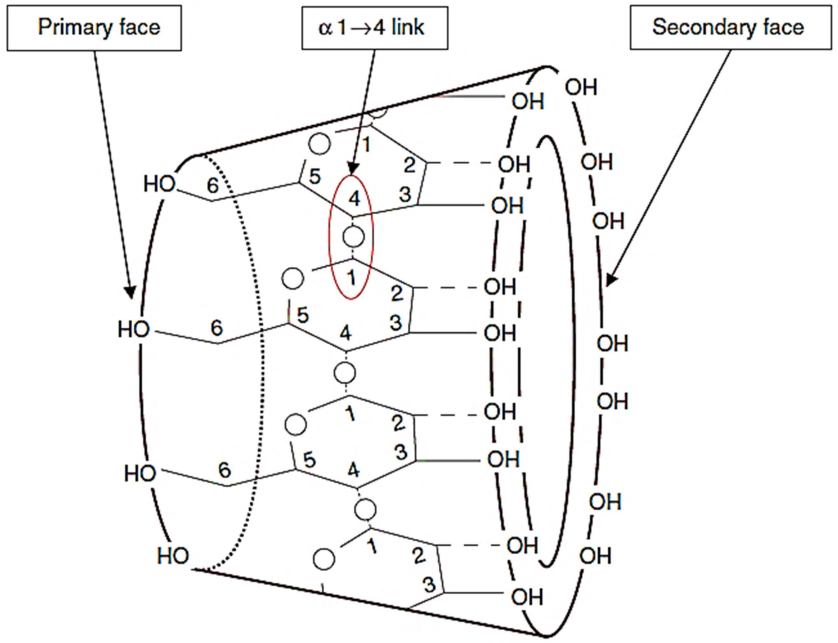

Figure (2): Structural arrangements of glucopyranose units in a γ-cyclodextrin, showing negatively charged hydroxyl groups at the rims creating the primary and secondary faces ***(Welliver, 2007).***

Sugammadex is a modified γ-cyclodextrin specifically designed to encapsulate the muscle relaxant rocuronium. γ-cyclodextrins are cyclic oligosaccharide carbohydrates made of eight sugar molecules obtained from the degradation of starch ***(Bom et al., 2009).***

γ-cyclodextrin is a hydrophilic molecule with a lipophilic core that can encapsulate other lipophilic, preferably steroidal molecules. γ-cyclodextrins therefore have aqueous solubility, with the ability to bind lipophilic

drugs. Although the eight identical hydroxyl side chains of sugammadex were specifically designed to bind rocuronium, the other steroidal muscle relaxants, vecuronium and pancuronium, are also bound by sugammadex, albeit with a much lower affinity (the equilibrium affinity constant value of rocuronium for sugammadex is 25,000,000 M, while for vecuronium, is only 10,000,000 M, meaning that the affinity is 2.5 times higher for rocuronium compared with vecuronium ***(Akha et al., 2010)***.

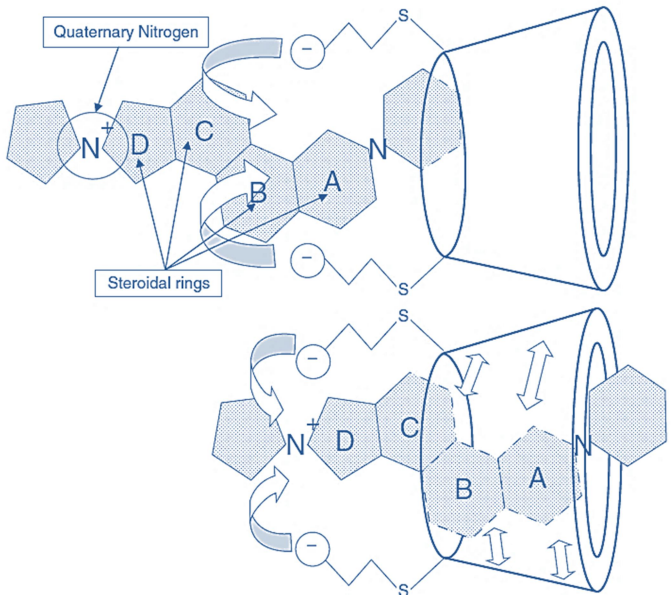

Figure (3): The encapsulation process: sugammadex carboxyl groups interact with the steroidal rings A, B, C, and D of the aminosteroid NMBA molecule drawing it into the cavity of the cyclodextrin where additional non-covalent attractions (⟺) hold the molecule securely in place ***(Welliver, 2007).***

One molecule of sugammadex is able to noncovalently bind one molecule of steroidal muscle relaxant. This binding is further increased by acid groups (COO–), which add an additional electrostatic bond interaction with the positively charged nitrogen of the muscle relaxant. No affinity exists to other muscle relaxants, like succinylcholine, mivacurium, atracurium, or cisatracurium ***(Akha et al., 2010)***.

Pharmacokinetics:

When sugammadex is intravenously injected (central compartment), it immediately binds free intravascular rocuronium. This leads to a concentration gradient, which shifts rocuronium from the peripheral compartment (including the effect compartment, i.e., the neuromuscular junction) towards the central compartment, where it is also encapsulated by sugammadex. This rapidly restores neuromuscular transmission and muscle function. A higher sugammadex dose is therefore more effective to lower the free rocuronium concentration in the plasma than a lower one ***(Akha et al., 2010)***.

In a dose range of 0.1 to 16 mg/kg, the pharmacokinetics of sugammadex shows a linear, dose-dependent relationship ***(Merck et al., 2013).***

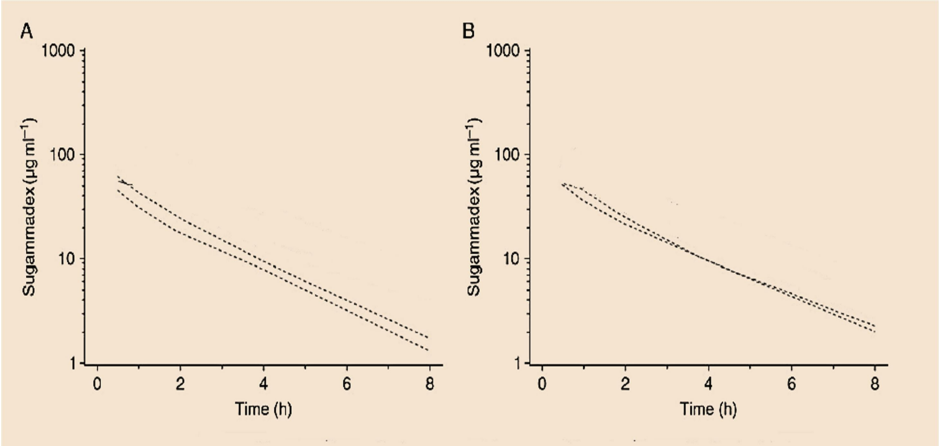

Figure (4): Semi log plots of plasma concentrations of sugammadex vs time after simultaneous administration with rocuronium 1.2 mg kg (A) or vecuronium 0.1 mg kg (B) ***(Cammu et al., 2007).***

The elimination half-life of sugammadex is approximately 100–150 minutes. It is not metabolized in the body and is nearly 100% cleared by the kidneys, with a clearance of about 75–120 mL/min, which equates to the normal glomerular filtration rate. Sugammadex is rapidly excreted from the body: a study using radioactive labelled-sugammadex showed that in healthy volunteers, 70% of the dose was excreted in 6 hours and over 90% in 24 hours ***(Peeters et al., 2011).***

Other data suggests an excretion of 59% to 80% in 24 hours. It is of clinical relevance to note that in the presence of sugammadex, the hepatic biotransformation and final clearance, via biliary excretion, of rocuronium is changed to a completely different (liver-independent) renal pathway. As a result, special consideration must be given to patients with renal failure. Although sugammadex works as efficiently as in patients with normal renal function, i.e., the mechanism of action of sugammadex is independent of renal perfusion ***(Staals, 2011).***

Only 29% of the sugammadex–rocuronium molecules are cleared in 72 hours in end-stage renal failure. ***(Staals, 2010)***

Although no cases of reoccurrence of neuromuscular block using 2 mg/kg sugammadex at a return of T2 (2nd twitch of TOF stimulation) in renal failure patients have been reported, the use of sugammadex is not recommended in patients with low creatinine clearance (<30 mL/min) or in need of dialysis, since the studies on this topic were not powered for safety ***(Merck et al., 2013).***

However, sugammadex can be dialyzed with the appropriate dialysis filter ***(Cammu et al., 2012).***

Clinical use and dosage:

Depending on the muscle relaxant used and the depth of the neuromuscular block at the time of reversal, different sugammadex doses are recommended. The doses should be able to accelerate the speed of recovery from the neuromuscular block to a TOF ratio of 0.9 in an average of 3 minutes. The different doses for rocuronium are summarized in table (1).

Table (1): Sugammadex doses for an average reversal time of 3 minutes in a rocuronium- induced neuromuscular block ***(Suy et al., 2007).***

Dose of sugammadex	Indication	Mean recovery time to TOF 0.9
16 mg/kg	immediate reversal after 1.2 mg/kg rocuronium	1.5 minutes
4 mg/kg	Routine reversal of deep neuromuscular block (PTC 1-2)	3 minutes
2 mg/kg	Routine reversal of moderate neuromuscular block (T2 appearance)	2 minutes
1 mg/kg	Reversal at reappearance of four twitches to TOF stimulation	2 minutes
0.22 mg/kg	Reversal at TOF 0.5	2 minutes

Abbreviations: PTC: posttetanic count, TOF: train of four count.

There is no dose recommendation for the immediate reversal of a vecuronium-induced neuromuscular block. The

sugammadex doses to reverse a deep (posttetanic count [PTC] of 1–2) or a moderate (TOF count >2) vecuronium-induced neuromuscular block are the same as for rocuronium; however, due to the lower affinity, the speed of recovery from the neuromuscular block is slightly slower (3.3 minutes after 4 mg/kg sugammadex, at a PTC of 1–2 and 2.3 min after 2 mg/kg, at a TOF count >2 ***(Duvaldestin et al., 2010).***

Doses of up to 96 mg/kg sugammadex have been tested and did not show any adverse effects in healthy adults ***(Peeters et al., 2010).***

Specific patient groups:

Obesity:

In obese patients, the dose of rocuronium is calculated according to ideal body weight ***(Gaszynski et al., 2011).***

Whereas it is recommended to dose sugammadex according to actual body weight ***(Merck et al., 2013).*** Interestingly, a dose of sugammadex calculated according to ideal body weight seems to be insufficient to reverse deep and moderate neuromuscular blocks in morbidly obese patients ***(Llauradó et al., 2012)***.

While a dose calculated according to ideal body weight +40% was shown to be effective in a clinical study (mean reversal time <2 min) ***(Van Lancker et al., 2011)*** A final consensus on optimal sugammadex dosing in obese patients has not been reached so far ***(Schmartz et al., 2013).***

However, neuromuscular monitoring is recommended in all cases since a reoccurrence of the neuromuscular block is possible in obese patients receiving inadequate doses of sugammadex ***(Le Corre et al., 2011).***

Safety:

The most clinically relevant common side effects (>2%) of sugammadex are due to the fast recovery of the muscle function during balanced anaesthesia, which might unmask a too light anaesthesia. In such cases, the patient might cough, move, grimace, or suckle on of the endotracheal tube ***(Merck et al., 2013).***

QT-Prolongation has been a concern since there has been a report of possible QT prolongation and one case of atrioventricular block after sugammadex ***(de Boeret al., 2007).***