Sugammadex : Sugammadex is a modified γ-cyclodextrin designed to encapsulate aminosteroidal NMBA molecules. It provides fast and reliable reversal of these drugs. However, it cannot reverse the neuromuscular blockade induced by benzylisoquinolinium NMBAs or succinylcholine.

The center of the ring-shaped molecule is hydrophobic, whereas the periphery is hydrophilic because of the eight side chains that are attached to the original γ-cyclodextrin molecule. Each side chain has a negatively charged carboxyl group that attracts the positively charged nitrogen ions of the NMBA molecules, and the hydrophobic core encloses the body of the NMBA molecule. Sugammadex exerts its action in the plasma, where it forms a 1-to-1 complex with steroidal NMBA molecules. As the concentration of free NMBA molecules decreases in the plasma, NMBA molecules leave the neuromuscular junction and move along their concentration gradient to the bloodstream, where they are encapsulated by available free sugammadex molecules. Sugammadex was originally designed to reverse rocuronium blockade, but it has a higher affinity for pipecuronium and a lower affinity for vecuronium and pancuronium molecules. Sugammadex has an association constant that is 3.1 times lower for vecuronium than for rocuronium. Therefore reversal of vecuronium-induced blockade by sugammadex may take longer than reversal of rocuronium-induced blockade. The lower affinity for vecuronium, however, is partly offset by the greater potency of vecuronium compared with rocuronium, which leads to administration of fewer molecules of vecuronium than of rocuronium (at equivalent doses). Nonetheless, sugammadex can reverse vecuronium-induced blockade faster and more reliably than neostigmine.

Because sugammadex is characterized as a drug of low distribution, it encapsulates the aminosteroid only in the plasma rather than binding it within the extravascular space. Encapsulation in the plasma results in a new relaxant equilibrium between the two areas. Movement continues of the unbound aminosteroid back into the plasma, where sugammadex is available to bind. This diffusion of the neuromuscular blocker away from the site of action, trapping it within the plasma, results in a rapid, stable reversal. Provided a sufficient sugammadex dose is administered to cause extravascular diffusion and encapsulation in the plasma of the aminosteroid, partial recovery is not required before administration.

Sugammadex is highly water soluble, and its volume of distribution approximates the extracellular fluid volume. Therefore many advocate that the dose of sugammadex be based on the actual body weight for morbidly obese patients, or at least basing the dose on ideal body weight + 40%. Regardless of the dosing regimen in this at-risk population, quantitative monitoring is recommended to confirm recovery before tracheal extubation.

Sugammadex is weakly metabolized, and the sugammadex-muscle relaxant complex is excreted unchanged almost exclusively via urine. The elimination half-life is approximately 100 minutes; therefore the majority of the complexes are excreted from the body in 8 h (assuming normal renal function). Kidney failure slightly prolongs reversal times, but sugammadex is currently not approved for patients with end-stage renal disease. If needed, sugammadex and the sugammadex-rocuronium complex can be removed via high-flux dialysis.

Sugammadex does not influence ACh concentrations; therefore it is free of the muscarinic side effects of cholinesterase inhibitors. Early reports raised questions about potential arrhythmogenic properties, but later data did not confirm this finding. In a recent meta-analysis, sugammadex proved superior to neostigmine because it reversed the neuromuscular block faster and more reliably, with fewer adverse events. Better respiratory outcomes and higher patient satisfaction were also described in sugammadex-neostigmine comparative investigations. Unlike cholinesterase inhibitors, sugammadex reversal is not influenced by the type of anesthesia. It is equally effective after propofol-opioid (total intravenous anesthesia) or inhalation anesthetic agents. Sugammadex has a well-defined dosing scheme to antagonize rocuronium blockade, based on the level of neuromuscular blockade.

Although anticholinesterases are contraindicated in the reversal of profound and deep neuromuscular block, sugammadex can rapidly (within 2 to 5 min) and reliably reverse all depths of neuromuscular blockade induced by rocuronium without major side effects. Sugammadex can be used in “can't-intubate-can't-ventilate” (CICV) situations by administering a large dose (16 mg/kg), as long as other coadministered anesthetic agents (propofol, benzodiazepines, opioids) do not prevent spontaneous ventilation. The rocuronium reversal

time in this scenario is faster with sugammadex than the spontaneous recovery from succinylcholine block. However, pharmacologic reversal of neuromuscular blockade with sugammadex cannot reliably prevent hypoxic events in the CICV scenario, and appropriate interventions focusing on airway patency, oxygenation, and ventilation are still paramount. During deep neuromuscular blockade (TOF count 0, post-tetanic count ≥ 1), treatment with 4 to 8 mg/kg sugammadex is recommended; after return of the first twitch to TOF stimulation (TOF count 1), a dose of 2 mg/kg sugammadex is required for antagonism (see Table 61.1). According to currently available evidence, during shallow (TOF count ≥ 4) and minimal neuromuscular block, further dose reductions (≤1 mg/kg) have been reported to be effective. It has to be emphasized that the use of sugammadex does not reliably prevent residual weakness unless the appropriate dose is chosen based on the depth of neuromuscular block assessed objectively. Because sugammadex has the highest affinity for rocuronium, it can be used for immediate reversal of this agent only. In this case, 3 minutes after a bolus dose of 1.2 mg rocuronium, 16 mg/kg is effective for reversal.

Side effects: The introduction of sugammadex to the U.S. market was delayed due to the U.S. Food and Drug Administration about the potential for hypersensitivity and anaphylaxis. A recent large-scale Japanese database analysis estimated the prevalence of sugammadex anaphylaxis as 0.039%, which approximates the prevalence of succinylcholine and rocuronium anaphylaxis (0.048% and 0.04%, respectively). Most case reports describe Ig-E mediated anaphylaxis after a patient's initial exposure to sugammadex. It is theorized that this reaction occurs as patients are sensitized via exposure to cyclodextrins that are used as preservatives in food, cosmetics, and other medications. In most cases, anaphylaxis occurs within 5 min after sugammadex administration and results in profound hypotension, tachycardia, and rash. Although anaphylaxis is not dose dependent, this phenomenon has been described more frequently with administration of 16 mg/kg sugammadex. Anaphylactic reactions should be treated aggressively with epinephrine and intravenous fluids.

Marked bradycardia has also occurred after administration. Interestingly, this is not related to any cholinergic mechanism, as expected with acetylcholinesterase inhibition, and it appears dose related. Standard treatments, depending on severity, can be used to manage these more

troubling adverse effects. Reported effects on coagulation have also occurred, likely as a result of factor Xa inhibition by sugammadex identified in vitro; this effect is considered transient and does not normally appear to require treatment. Because sugammadex is a selective relaxant binding agent, there are some considerations unique to this drug. Use of doses lower than recommended may result in reblockade due to insufficient drug to bind and to keep to the aminosteroid in the plasma. Additionally, recurrence of neuromuscular blockade can occur if another drug displaces it from the complex. Toremifene has been identified as a drug that can displace an aminosteroid from sugammadex. Another drug-drug interaction of concern is the ability of sugammadex to lower the concentration of all types of hormonal contraceptives, including pills, injections, implants, patches, rings, and intrauterine devices. If a woman is currently using a hormonal method of contraception and sugammadex is administered, an additional form of contraception is required for the next 7 days. Finally, sugammadex is physically incompatible with several drugs (e.g., ondansetron) and the line should be flushed in between these agents. Complete review of the product information supplied by the manufacturer for sugammadex is encouraged.

Furthermore, it is advised to postpone flucloxacillin administration for 6 h after sugammadex administration to preserve its action.

Consideration should also be given to the possible need for another neuromuscular blocking agent a relatively short time after the use of sugammadex for rocuronium or vecuronium reversal. Several factors, including dose of agent, length of time, and renal function, will assist in the decision. Successful neuromuscular reblockade can be achieved within 5 min with 1.2 mg/kg rocuronium as long as no more than 4 mg/kg sugammadex was originally used for reversal. In individuals with normal renal function, 4 h should elapse before readministration of 0.6 mg/kg rocuronium or 0.1 mg/kg vecuronium. However, as the sugammadex complex is eliminated by the kidney, it is recommended in patients with mild or moderate renal impairment (creatinine clearance 30 to 80 mL/min), to wait 24 h before readministration. Because sugammadex does not affect benzylisoquinolones, these can be used during the waiting period, even if a very large (16 mg/kg) dose was used in the previous 24 h.

Considerations in Select Populations The sugammadex-aminosteroid complex is excreted by the kidney; therefore renal impairment will alter its disposition. For patients with mild or moderate renal impairment, the usual recommended dose for the given situation should be administered. Although sugammadex will result in effective reversal, it is not currently recommended by the manufacturer for use in severe renal impairment (creatinine clearance < 30 mL/min) or for patients requiring dialysis. In geriatric patients without severe renal impairment, the usual adult dose should be administered; however, recovery times may be longer. Because all doses are currently based on actual body weight, the amount required and available for use should be considered in obese patients. Currently, sugammadex is not approved by the U.S. Food and Drug Administration for use in pediatric patients. However, in the European Union, approval for routine reversal has been given for children and adolescents (2 to 17 years). In this case, administration of 2 mg/kg at recovery to T2 is approved only for rocuronium-induced block reversal.