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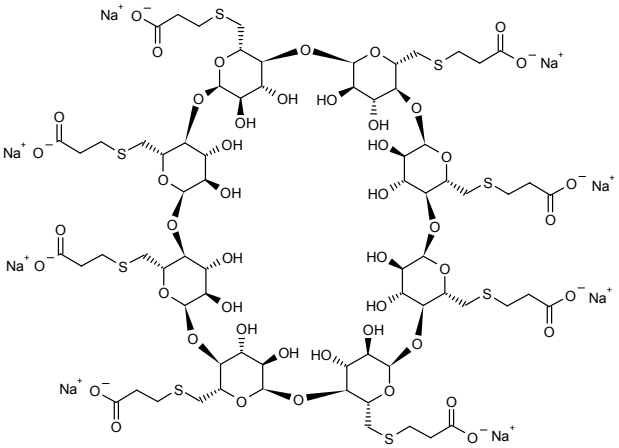
Sugammadex Sodium

Agent for Reversal of Neuromuscular Blockade

Prop INN; USAN

ORG-25969

6A,6B,6C,6D,6E,6F,6G,6H-Octakis-S-(2-carboxyethyl)-6A,6B,6C,6D,6E,6F,6G-octasulfanyl-γ-cyclodextrin octasodium salt



$C_{72}H_{104}Na_8O_{48}S_8$
Mol wt: 2178.0135
CAS: 343306-79-6
CAS: 343306-71-8 (as free acid)
EN: 306386

Abstract

The use of neuromuscular blocking agents is well established in anesthetic practice. Reversal of residual blockade at the end of surgery is essential to ensure full recovery of neuromuscular function and to avoid any residual paralysis. Chelation or chemical encapsulation has emerged as a novel mechanism in the reversal of neuromuscular blockade, and the investigation of cyclodextrins resulted in the discovery of sugammadex, a chemically modified γ-cyclodextrin. Sugammadex forms a very tight host-guest complex with rocuronium, resulting in the selective reversal of neuromuscular blockade induced by this agent and other steroidal neuromuscular blockers. The efficacy and safety of sugammadex have been demonstrated *in vitro* and *in vivo* and clinical studies have shown that sugammadex is well tolerated and effective as a reversal agent for neuromuscular block induced by rocuronium. The agent is in late-stage clinical development.

Synthesis

Halogenation of γ-cyclodextrin (I) with iodine or bromine and triphenylphosphine in DMF provides the halogen derivative (II), which is submitted to nucleophilic displacement of the halogen atoms by treatment with either 3-mercaptopropionic acid and NaH in DMF (1) or with 3-mercaptopropionic acid methyl ester and $CsCO_3$ in DMF followed by hydrolysis with NaOH (2). Scheme 1.

Introduction

Neuromuscular blocking drugs, or skeletal muscle relaxants, are widely used as nonanesthetic adjuncts in surgical procedures and in critically ill patients to facilitate tracheal intubation, mechanical ventilation and surgical access. Neuromuscular blockers are classified according to their mechanisms of action as either depolarizing or nondepolarizing. There is a clinical preference for nondepolarizing neuromuscular blockers because they are associated with fewer side effects than the depolarizing drugs. Nondepolarizing neuromuscular blockers act as competitive antagonists of the nicotinic acetylcholine (ACh) receptor at the neuromuscular junction, thus preventing cell membrane depolarization. They include cisatracurium, mivacurium, pancuronium, vecuronium and rocuronium (3, 4).

Antagonism or reversal of residual neuromuscular blockade at the end of surgery is essential to ensure full recovery of neuromuscular function. This reversal avoids any postoperative complications associated with residual paralysis (5). Traditionally, antagonism of nondepolarizing neuromuscular blockade is achieved with acetylcholinesterase (AChE) inhibitors, but this is associated with side effects and other limitations, and is not suitable for reversing depolarizing agents. Chemical encapsulation of the neuromuscular blocker has emerged as a novel pharmacological approach to the reversal of neuromuscular blockade. Cyclodextrins are cyclic oligosaccharides that are able to encapsulate lipophilic molecules such as steroids, and could therefore be used to sequester and

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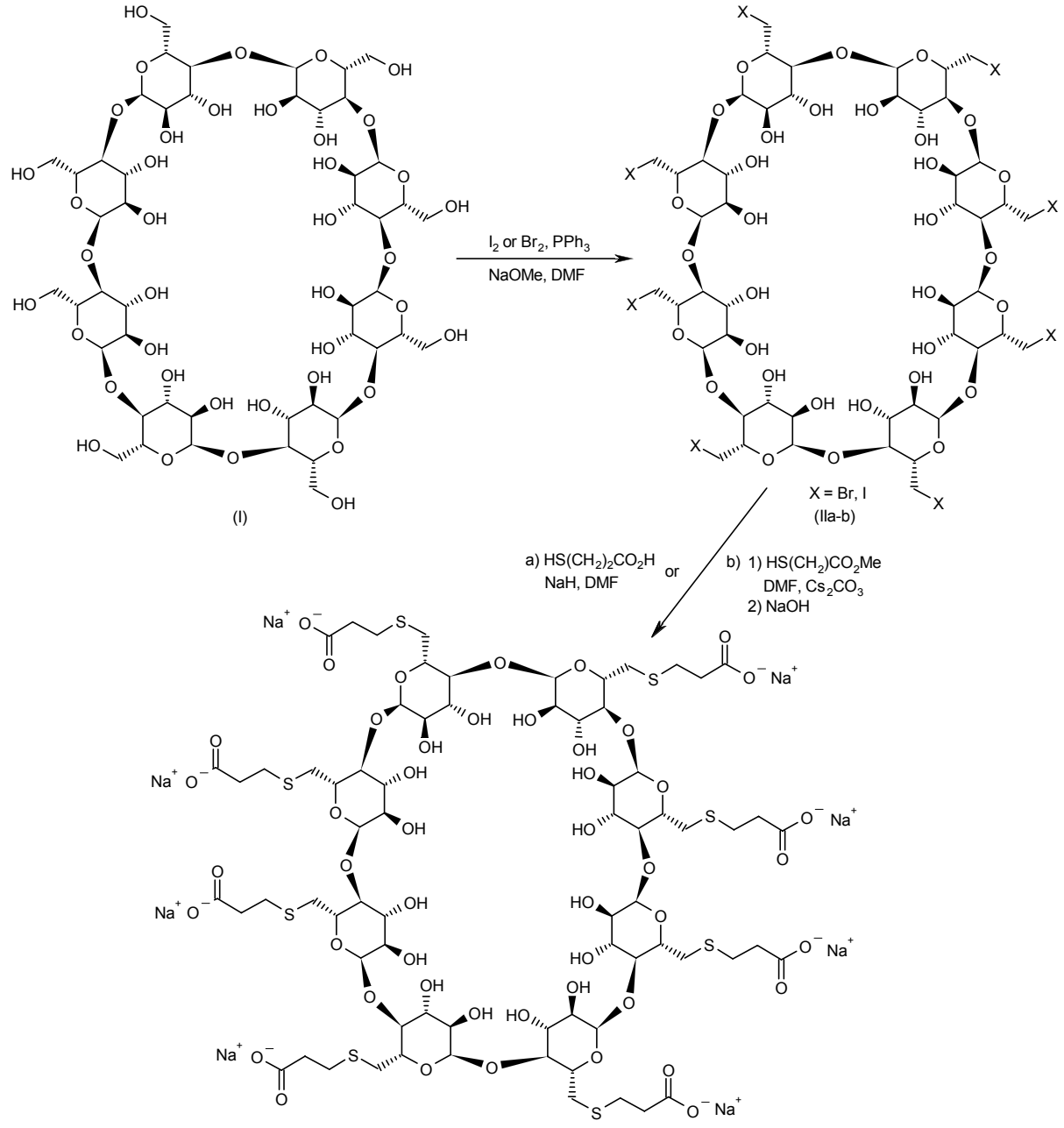
Scheme 1: Synthesis of Sugammadex Sodium



promote the dissociation of neuromuscular blockers from their site of action, and reverse the action of both depolarizing and nondepolarizing agents without the side effects of AChE inhibition. Sugammadex (Org-25969) is a chemically modified γ-cyclodextrin that is able to encapsulate all four steroidal rings of rocuronium within its lipophilic cavity, thereby preventing its access to the nicotinic receptor and promoting its dissociation therefrom (2, 6-10). Sugammadex is in late-stage clinical development for the reversal of neuromuscular blockade (11).

Pharmacological Actions

Sugammadex forms a very tight 1:1 host-guest complex with rocuronium, with an association constant (K_a) of approximately 10^7 M^{-1}. Nuclear magnetic resonance and X-ray crystallography studies demonstrated that the complex is a true inclusion complex, with the steroid located inside the central void of the cyclodextrin (2, 8, 12, 13).

The selective reversal by sugammadex of neuromuscular blockade induced by steroidal neuromuscular block-

ers was demonstrated *in vitro* in the mouse hemidiaphragm preparation. A 90% blocking dose (3.6 μM) of rocuronium was administered after a stimulation period of 30 min. Administration of increasing doses of sugammadex 20 min later revealed an EC_{50} (concentration to recover 50% of muscle contraction) of 1.2 ± 0.8 μM. A maximum reversal of 95% was achieved at the concentration of 3.6 μM, equivalent to the rocuronium concentration. Sugammadex also effectively reversed neuromuscular blockade induced by rapacuronium, vecuronium and pancuronium. Following induction of profound block by administration of 3 x the ED_{90} dose (*i.e.*, 10.8 μM) of rocuronium, sugammadex was also able to reverse the block (62 ± 9%), in contrast to neostigmine which had no effect (2, 8, 14).

The effects of sugammadex were studied *in vivo* in anesthetized guinea pigs. The sciatic nerve was stimulated and the force of gastrocnemius contractions was measured. Infusions of neuromuscular blockers were given to obtain a steady-state 90% neuromuscular block. Following i.v. bolus injections of sugammadex 1 mg/kg, a rapid reversal of neuromuscular block induced by steroidal neuromuscular blockers was observed, with a 90% recovery of twitch height obtained within 1 min; it was less active against nonsteroidal neuromuscular blockers. After 90% neuromuscular block with rocuronium, rapacuronium, pancuronium and vecuronium, spontaneous recovery occurred in 2.5, 2.1, 7.4 and 12.9 min, respectively. Following administration of sugammadex, recovery occurred in 0.3-0.4 min for all drugs. There were no significant changes in heart rate or blood pressure (15, 16). The effect of sugammadex against profound block induced by administration of 10 x the ED_{90} dose of rocuronium was also evaluated in anesthetized guinea pigs. One minute after complete block developed, the administration of sugammadex 5 mg/kg i.v. resulted in rapid reversal of the neuromuscular block, with 90% recovery after 9.3 min (16).

In anesthetized cats, the effects of sugammadex were evaluated on rocuronium-induced steady-state block of the tibialis muscle. Following administration of rocuronium as a bolus and an infusion to produce a stable 90% block of twitch tension, sugammadex 1 mg/kg was given. This resulted in a rapid reversal of neuromuscular block, with 90% recovery in 1.5-2.2 min compared with 7-9 min for spontaneous recovery. No significant changes in heart rate or mean blood pressure were seen (2, 16, 17).

The ability of sugammadex to reverse neuromuscular blockade of the ulnar nerve of the right thumb was investigated in anesthetized rhesus monkeys. A steady-state block was achieved with a bolus injection and infusion of rocuronium or vecuronium. Neuromuscular recovery was significantly faster following administration of sugammadex 1 mg/kg compared to spontaneous recovery after either rocuronium- or vecuronium-induced block ($p < 0.05$). There were no significant changes in heart rate or blood pressure (16, 18).

The reversal of neuromuscular blockade and the simultaneous increase in plasma rocuronium concentration following the administration of sugammadex were demonstrated in anesthetized guinea pigs using a liquid chromatography/mass spectrometry method. Rocuronium was infused to produce a steady-state 90% neuromuscular block. After 30 min, a concomitant infusion of either sugammadex or saline was started. In the sugammadex-treated group there was a significant increase in twitch height of the gastrocnemius muscle, whereas in the saline-treated group no significant changes in twitch height were observed. A marked increase in plasma concentrations of rocuronium, both free and complexed to sugammadex, was observed after 50 and 60 min of infusion of rocuronium (corresponding to 20 and 30 min after the start of the sugammadex infusion). The authors concluded that the reversal of neuromuscular blockade by sugammadex could be explained by the rapid transfer of free rocuronium from the effect compartment (neuromuscular junction) to the central compartment (bound in plasma), explaining the increase in total plasma concentrations of rocuronium (19, 20).

A study in anesthetized cats demonstrated that the rapid reversal of rocuronium-induced neuromuscular block was not dependent on the rapid renal excretion of the sugammadex-rocuronium complex. Single twitch contractions of the tibialis muscle were studied in cats before and after ligation of both renal arteries. There was a markedly more rapid reversal of rocuronium-induced neuromuscular block in renal artery-ligated cats administered sugammadex 2.3 μmol/kg, with 90% recovery in 4.6 min compared with 31.6 min in the intact animals, providing further evidence that sugammadex reversal of neuromuscular blockade induced by rocuronium is attributable to the formation of a sugammadex-rocuronium complex (21).

The effects of acid-base status on the reversal of rocuronium-induced neuromuscular block by sugammadex were investigated in anesthetized guinea pigs. Metabolic and respiratory acidosis or alkalosis was induced in guinea pigs, and spontaneous recovery and sugammadex-induced recovery of gastrocnemius contractions were compared under different acid-base conditions. The recovery after administration of sugammadex was complete within 1 min and was unaffected by the acid-base status (22).

A further study using mouse isolated phrenic nerve hemidiaphragm preparations was conducted to evaluate the potency and efficacy of nonsteroidal neuromuscular blocking agents when administered after reversal of rocuronium-induced neuromuscular block by sugammadex. Hemidiaphragm preparations were treated with cumulative concentrations of atracurium, cisatracurium, mivacurium or succinylcholine. All the agents caused complete block and their potency tended to increase following pretreatment with rocuronium and sugammadex. A statistically significant improvement in potency was observed for atracurium and succinylcholine. These results have relevance in case emergency reintubation is required following the administration of sugammadex (23).

Pharmacokinetics

The plasma pharmacokinetics of sugammadex were determined in guinea pigs. Bolus doses of sugammadex of 0.15, 0.5 or 1.0 mg/kg were administered following achievement of a stable 90% neuromuscular block with rocuronium. Plasma levels declined in a biphasic manner. The pharmacokinetics of sugammadex were characterized by low distribution and a short elimination half-life. There was a dose-related increase in urinary excretion of sugammadex, which appeared to be mainly due to glomerular filtration. Rocuronium appeared to decrease the distribution of sugammadex (20).

Clinical Studies

A randomized phase I study investigating the safety, pharmacokinetics and efficacy of sugammadex was performed in 29 healthy male volunteers. Ten subjects received general anesthesia on two occasions using remifentanil and propofol for induction and maintenance, and an intubating dose of 0.6 mg/kg rocuronium bromide. At maximum block 3 min after administration of rocuronium, placebo or sugammadex (0.1-8.0 mg/kg) was given. Adverse events related to administration of sugammadex were generally mild and of limited duration. There were no clinically relevant changes from baseline in routine laboratory parameters, ECG, physical examination or vital signs. In the subjects (n=2) given sugammadex 4.0 mg/kg, recovery of neuromuscular block was achieved in 2.5 and 3.2 min, and in the subjects (n=2) given 8.0 mg/kg, the recovery times were 1.0 and 1.2 min. The corresponding values in subjects administered placebo (n=10) were 35-69 min. No signs of recurarization (re-establishment of neuromuscular blockade) were observed up to 90 min after administration of sugammadex. This preliminary assessment indicated that sugammadex was well tolerated and effective as a reversal agent for profound neuromuscular block induced by rocuronium (24). On the basis of the clinical data from this phase I study, a mechanism-based pharmacokinetic/pharmacodynamic (PK/PD) model was developed. The model accurately predicted the PK and PD of the rocuronium-sugammadex interaction and could be used to investigate potential drug-drug interactions with sugammadex (25-27).

In a phase II, dose-response study, 87 patients aged 18-80 years received 1.0 mg/kg rocuronium to induce profound neuromuscular block. Sugammadex (2-16 mg/kg) or placebo was administered either 3 or 15 min later. The mean time to recovery was 2.5 min for a dose of 8 mg/kg. No serious adverse events were reported (11).

Another phase II study investigated the dose-response relationship of sugammadex following prolonged rocuronium-induced neuromuscular block. Thirty adult patients who had an anticipated duration of anesthesia of at least 2.5 h were randomized to receive sugammadex doses of 0.5-6.0 mg/kg to reverse neuromuscular block. There was a dose-related decrease in the time to recovery. Regression analysis showed that the fastest achievable time to recovery was 1.6 min. Sugammadex was well tolerated and there was no evidence of recurarization (11).

The safety and efficacy of sugammadex 2.0 mg/kg in reversing rocuronium-induced neuromuscular block were evaluated in patients randomized to either propofol or sevoflurane maintenance anesthesia after induction of anesthesia with propofol. Forty-two patients with an anticipated duration of anesthesia of > 45 min were enrolled in this phase II study. The mean time from sugammadex administration to recovery was 1.83 min for patients in the propofol group *versus* 1.80 min in patients switched to sevoflurane. These results were within the predefined range for equivalence. No recurarization was observed (11).

Phase III trials are expected to start soon and will involve approximately 1,500 patients. Reversal of neuromuscular block will be assessed following administration of rocuronium and vecuronium. The results are anticipated in 2006 (11, 28).

Source

Organon International (NL).

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