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Neuromuscular transmission: New concepts and agents

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Abstract Sugammadex is the first selective relaxant binding agent which was originally designed to reverse the steroidal NMB drug rocuronium. The results of recent studies demonstrate that sugammadex is effective for reversal of rocuronium and vecuronium-induced neuromuscular block without apparent side-effects. This is in contrast to the currently available cholinesterase inhibitors used to reverse neuromuscular block and which are even ineffective against profound neuromuscular block and have a number of undesirable side-effects. Sugammadex-rocuronium complexes are highly hydrophilic and it has been demonstrated that sugammadex is excreted in a rapid and dose-dependent manner in urine, resulting in a complete elimination from the body. The ability of sugammadex to reverse rocuronium and vecuronium-induced neuromuscular block may have major implications for routine anesthetic practice. Once sugammadex becomes commercially available, anesthesiologists will be capable of maintaining the desired depth of neuromuscular block at any time, thereby assuring optimal surgical conditions. The mechanism by which sugammadex encapsulates rocuronium and vecuronium appears to be superior to currently used neuromuscular block reversal strategies in terms of speed, efficacy and side effects. In this article, clinical studies of sugammadex are discussed.

1. Introduction

Neuromuscular management is important in clinical anesthesia and emergency medicine. Neuromuscular blocking agents (NMBAs) provide significant contributions such as optimal surgical conditions and a reduced incidence of laryngopharyngeal lesions due to tracheal intubation [1]. However, the use of NMBAs agents is still associated with higher morbidity and mortality compared with techniques that avoid NMBAs [2]. The main causal factor of these complications is postoperative residual curarization (PORC) [3-5]. One of the challenges in clinical anesthesia is to avoid PORC and to reduce its incidence by improving monitoring of the recovery from neuromuscular block (NMB) or by efficient reversal. Reversal of NMB is the best strategy to facilitate rapid and complete recovery after surgery, and it may reduce the incidence of severe morbidity and mortality associated with anesthesia management [2]. However, reversal of NMB with cholinesterase inhibitors (in combination with muscarinic antagonists) has limitations due to its mechanism of action (ineffective against profound NMB) and, moreover, unwanted side effects. Thus, there is clearly a clinical need for a new reversal agent, with minimal side effects and the capability to reverse NMB effectively, independently of its depth. Sugammadex is the first selective relaxant binding agent that can reverse the effects of the NMBA rocuronium and vecuronium and led to positive results in preclinical studies. The mechanism of action of sugammadex is characterized by a completely different mechanism of action compared with the

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currently used combination of cholinesterase inhibitors and muscarinic antagonists. This particular mechanism is promising to solve both shortcomings of the cholinesterase inhibitors: their side effects and limitations for the depth of block that can be reversed. In this article, clinical studies of sugammadex are discussed.

2. Efficacy and safety of sugammadex

The first human exposure of sugammadex was reported by Gijsenbergh et al [6]. Twenty-nine healthy male volunteers received either sugammadex or placebo. In the first part of the study, 19 subjects received sugammadex up to 8.0 mg/kg or placebo without administration of a NMBA. In the second part of this study, the subjects were anesthetized and received dose of 0.6 mg/kg rocuronium, followed by intubation and mechanical ventilation. This was followed by a single bolus injection of sugammadex (0.1-8.0 mg/kg) or placebo. Assessment of efficacy showed a significant reduction in recovery time after the treatment with sugammadex as compared with placebo. A dose of sugammadex of 8.0 mg/kg resulted in a recovery time to a train-of-four (TOF) ratio of 0.9 of 1 minute compared with 52 minutes for placebo. Neither residual blockade nor recurarization was observed. There were no adverse events, and sugammadex was well tolerated in doses up to 8.0 mg/kg. Shields and colleagues [7] studied sugammadex for reversal of prolonged rocuronium-induced NMB. Thirty patients were anesthetized and received rocuronium 0.6 mg/kg as an initial dose followed by increments to maintain a deep NMB. After at least 2 hours of NMB, at recovery of the second twitch (T_2) of the TOF ratio, the patients received sugammadex in a randomly assigned dose between 0.5 and 6.0 mg/kg. The results showed that increasing doses of sugammadex reduced the mean recovery time from 6.49 minutes (0.5 mg/kg sugammadex) to less than 3 minutes in a dose-related manner. No signs of recurarization were observed and no adverse events were reported. The conclusion of this study was that the effective dose to reverse a deep and prolonged rocuronium-induced NMB appears to be 2 to 4 mg/kg.

Sorgenfrei and others [8] investigated the dose-response, safety, and pharmacokinetics of sugammadex in a dose from 0 (placebo) up to 4.0 mg/kg in reversing NMB induced by 0.6 mg/kg rocuronium. Sugammadex, administered at reappearance of T_2 of the TOF ratio, decreased the reversal time in a dose-dependent manner from 21.0 minutes in the placebo group to 1.1 minutes in the 4.0 mg/kg sugammadex dose group. No signs of recurarization or other adverse events were observed. Two patients experienced hypotension after the administration of 2.0 and 3.0 mg/kg sugammadex. These adverse events were considered to be possibly related to sugammadex. Reversal of high-dose rocuronium (1.0 mg/kg) by sugammadex at 3 and 15 minutes after the administration of rocuronium was evaluated in another study by Khunl-Brady et al [9]. The patients were treated for the reversal of NMB with either placebo or sugammadex in a dose up to 16.0 mg/kg. This study showed that a profound rocuronium-induced NMB was on average reversed within 2.5 minutes for a dose of 8.0 mg/kg sugammadex or higher. Another study, by Vanacker et al [10], investigated the efficacy of sugammadex in reversing rocuronium-induced (1.0 mg/kg) NMB with either sevoflurane or propofol maintenance anesthesia: in both cases, a recovery time of 1.8 minutes was reported, excluding a difference larger than 0.5 minutes. After 2.0 mg/kg sugammadex, recovery to a normal neuromuscular function was equivalent under propofol and sevoflurane maintenance anesthesia. A multicenter dose-finding and safety study performed by de Boer et al [11] investigated the reversal of rocuronium-induced profound NMB by sugammadex at 5 minutes after the administration of rocuronium. After a high-dose rocuronium (1.2 mg/kg) for intubation, the patients received either placebo or sugammadex in a dose op to mg/kg 5 minutes after the injection of rocuronium. A dose of sugammadex of 16.0 mg/kg resulted in a recovery time of less than 2 minutes compared with 122 minutes for placebo. Residual blockade or recurarization was not observed. Sugammadex caused a dose-dependent, fast, and efficient reversal of profound rocuronium-induced NMB. Evaluation of safety data indicates that sugammadex is well tolerated at doses up to 16.0 mg/kg. Suy and coworkers [12] evaluated the dose-response relationship of sugammadex for the reversal of shallow rocuronium and vecuronium-induced NMB. Thirty-nine patients received 0.6 mg/kg rocuronium and 40 received 0.1 mg/kg vecuronium. Both groups were treated with either placebo or up to 4.0 mg/kg sugammadex (the vecuronium group up to 8 mg/kg) at reappearance of the T_2 of the TOF-ratio. Again, a normal neuromuscular function was the primary end point of this study. Sugammadex showed a fast and effective recovery after a rocuronium (1.7 minutes at 2 mg/kg sugammadex) and vecuronium-induced (1.5 at 4 mg/kg sugammadex) NMB. A clear dose-response relationship was observed. Again, residual blockade or recurarization was not reported. No adverse events related to sugammadex were reported and sugammadex showed a good safety profile. A multicenter study by Rex et al [13] further evaluated the efficacy of sugammadex in reversal profound NMB induced by 1.2 mg/kg rocuronium. Randomly at 3 or 15 minutes after the injection of rocuronium, sugammadex was administered in doses up to 16.0 mg/kg. A dose-dependent time to recovery to a normal neuromuscular function was found. The reversal time was significantly decreased compared to placebo. Only one adverse event was reported possibly related to sugammadex (QT prolongation).

An interesting study was conducted by Sacan and colleagues [14]. Reversal of rocuronium-induced NMB by sugammadex was compared with the reversal of the currently used combination of cholinesterase inhibitors and muscarinic acetylcholine receptor antagonists, neostigmine-glycopyrrolate and edrophonium-atropine. Sixty patients undergoing elective surgery with standardized