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Sugammadex rapidly reverses moderate rocuronium- or vecuronium-induced neuromuscular block during sevoflurane anaesthesia: a dose–response relationship

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Key points

- Sevoflurane anaesthesia has the potential to prolong NMB.
- The effect of sevoflurane on sugammadex reversal of rocuronium and vecuronium is explored.
- Sugammadex 0.5, 1.0, 2.0, or 4.0 mg was given on recovery of T_2.
- A clear dose–response relationship was found for both NMB drugs.
- This was similar to the doses described for total i.v. anaesthesia with propofol.

Background. Sugammadex shows a dose–response relationship for reversal of neuromuscular block (NMB) during propofol anaesthesia. Sevoflurane, unlike propofol, can prolong the effect of neuromuscular blocking agents (NMBAs), increasing recovery time. This open-label, randomized, dose-finding trial explored sugammadex dose–response relationships, safety, and pharmacokinetics when administered for reversal of moderate rocuronium- or vecuronium-induced NMB during sevoflurane maintenance anaesthesia.

Methods. After anaesthesia induction with propofol, adult patients were randomized to receive single-dose rocuronium 0.9 mg kg^{-1} or vecuronium 0.1 mg kg^{-1}, with maintenance doses as needed. Anaesthesia was maintained with sevoflurane. NMB was monitored using acceleromyography. After the last dose of NMBA, at reappearance of T_2, single-dose sugammadex 0.5, 1.0, 2.0, or 4.0 mg kg^{-1} or placebo was administered. The primary efficacy variable was time from the start of sugammadex administration to recovery of T_4/T_1 ratio to 0.9. Safety assessments were performed throughout.

Results. The per-protocol population comprised 93 patients (rocuronium, $n=46$; vecuronium, $n=47$). A statistically significant dose–response relationship was demonstrated for mean recovery times of T_4/T_1 ratio to 0.9 with increasing sugammadex dose with both NMBAs: rocuronium, 96.3 min (placebo) to 1.5 min (sugammadex 4.0 mg kg^{-1}); vecuronium, 79.0 min (placebo) to 3.0 min (sugammadex 4.0 mg kg^{-1}). Plasma sugammadex concentrations indicated linear pharmacokinetics, independent of NMBA administered. No study drug-related serious adverse events occurred. Evidence of reoccurrence of block was reported in seven patients [sugammadex 0.5 mg kg^{-1} (suboptimal dose), $n=6$; 2.0 mg kg^{-1}, $n=1$].

Conclusions. During sevoflurane maintenance anaesthesia, sugammadex provides well-tolerated, effective, dose-dependent reversal of moderate rocuronium- and vecuronium-induced NMB.

Keywords: reversal; rocuronium; sevoflurane; sugammadex; vecuronium

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Sugammadex (Bridion®, MSD, Oss, The Netherlands) is a modified γ-cyclodextrin developed specifically for the rapid reversal of neuromuscular block (NMB) induced by the steroidal neuromuscular blocking agents (NMBAs) rocuronium and vecuronium.[1–4] Preclinical and clinical data indicate a favourable efficacy and safety profile of sugammadex[1 5] when compared with current frequently used acetylcholinesterase inhibitor–anticholinergic drug combinations.

Studies of sugammadex have consistently shown that sugammadex rapidly and effectively reverses moderate and profound rocuronium-induced NMB in patients under propofol maintenance anaesthesia.[6–12] A dose-finding study in

patients receiving propofol maintenance anaesthesia has shown a dose-dependent decrease in time to recovery from moderate vecuronium-induced NMB.[4]

Sevoflurane is also widely used for the maintenance of anaesthesia[11] but, unlike propofol, sevoflurane has the potential to prolong the effect of NMBAs[13 14] and significantly increase time to recovery.[15] This randomized, controlled study explored the relationship between sugammadex dose and neuromuscular recovery under sevoflurane maintenance anaesthesia, when administered during moderate NMB [i.e. at reappearance of the second twitch (T_2)] after the administration of rocuronium or vecuronium. The pharmacokinetic and safety profiles of sugammadex were also evaluated.

Methods

This open-label, randomized, placebo-controlled, safety-assessor blinded, multicentre, Phase II, parallel group, dose-finding trial investigated 0.5, 1.0, 2.0, and 4.0 mg kg^{-1} sugammadex and placebo in combination with rocuronium or vecuronium. The study was conducted from September 2005 until March 2006, was approved by the Independent Ethics Committee of each trial centre, and was conducted in compliance with the current revision of the Declaration of Helsinki, the International Conference on Harmonization guidelines, and Good Clinical Practice and current regulatory requirements. All patients provided written, informed consent.

Patients were eligible for inclusion if they were Caucasian, aged $\geq$20 and $<$65 yr, categorized as ASA class I–III, and undergoing elective surgery requiring muscle relaxation in the supine position, under sevoflurane anaesthesia, with an anticipated duration of $\sim$1.5–3 h. Patients were excluded from the study if difficult intubation was anticipated; if they had a neuromuscular disorder that could impair NMB or significant renal or hepatic dysfunction; a (family) history of malignant hyperthermia; allergy to narcotics, NMBAs, or other medication used during general anaesthesia; or were receiving medication expected to interfere with the NMBA. Female patients who were pregnant, breastfeeding, or of childbearing potential not using an adequate method of contraception were also excluded, as were those who had participated in another trial within the previous 6 months.

Patients were allocated a subject number in sequential order of their enrolment into the trial. Randomization was performed by the study sponsor in blocks of five according to Good Clinical Practice guidelines. Each patient received a treatment code using a central randomization system that was part of a secured trial website. For the first block at each trial site, patients were randomly assigned to rocuronium or vecuronium and then to one of the sugammadex 0.5, 1.0, 2.0, or 4.0 mg kg^{-1} or placebo groups. In subsequent blocks, the NMBA was alternated and patients were randomized to a sugammadex dose or placebo.

An i.v. cannula was inserted into a forearm vein for administration of anaesthetic drugs, rocuronium or vecuronium, and sugammadex. A second i.v. cannula was inserted into the opposite arm for collection of blood samples for safety and pharmacokinetic analyses. Anaesthesia was induced with i.v. propofol plus an opioid (fentanyl, remifentanil, piritramide, or sufentanil) and optional nitrous oxide, and maintained using sevoflurane and an opioid (with optional nitrous oxide). Other anaesthetic practices were consistent with routine practices at the trial sites. Drugs and doses used for anaesthesia were adjusted to provide optimal patient care.

After anaesthesia induction but before NMBA administration, monitoring of neuromuscular activity was started using acceleromyography (TOF-Watch® SX, Organon Ireland Ltd, a division of Merck and Co., Inc., Swords, Co. Dublin, Ireland). Stabilization and calibration of the TOF-Watch® SX were performed according to good clinical research practice.[16] Repetitive train-of-four (TOF) stimulation was applied at the wrist ulnar nerve every 15 s until the end of anaesthesia, or at least until recovery of the T_4/T_1 ratio to 0.9. Neuromuscular data were collected via a transducer affixed to the thumb using the TOF-Watch® SX Monitoring Program (Organon Ireland Ltd, a division of Merck and Co., Inc.).

Rocuronium 0.9 mg kg^{-1} (three times ED_{95}, dose selected based on regulatory requirements) or vecuronium 0.1 mg kg^{-1} (two times ED_{95}) was administered as an i.v. bolus within 10 s into a fast-running venous infusion. Tracheal intubation was performed after NMBA administration. Maintenance doses of rocuronium 0.1–0.2 mg kg^{-1} (rocuronium group) or vecuronium 0.02–0.03 mg kg^{-1} (vecuronium group) were given as necessary to maintain the NMB depth at 25% of first twitch (T_1) or deeper.

After the last dose of NMBA and at reappearance of T_2, sugammadex (dose according to randomization) or placebo were administered as an i.v. bolus (within 10 s) into a fast-running saline infusion. Patients did not receive any other reversal agent or an NMBA other than rocuronium or vecuronium before recovery of the T_4/T_1 ratio to 0.9. Clinical assessments of recovery (5 s head lift, diplopia, tongue depressor test, and general muscle weakness) were performed in fully awake, orientated patients on admission to the recovery room.

For the pharmacokinetic assessment, nine blood samples (each 5 ml) were collected from each patient for the determination of plasma rocuronium, vecuronium, and sugammadex concentrations. Samples were collected before and 2, 5, and 15 min after administration of NMBA, and before and 2, 5, 15, and 60 min (or at the end of surgery) after administration of sugammadex or placebo. Drug plasma concentrations were determined by the Department of Bioanalytics, MSD, Oss, The Netherlands, using validated liquid chromatographic assay methods with mass spectrometric detection.[17] Assay methods for sugammadex, rocuronium, and vecuronium plasma concentrations could not distinguish between complexed and non-complexed sugammadex/NMBA.

Patients were monitored or questioned for adverse events (AEs) and serious AEs (SAEs) from the time of NMBA administration until the seventh postoperative day. All AEs and SAEs were coded using Medical Dictionary for Regulatory Activities (MedDRA; version 9.0). At the second