CLINICAL TRIAL

Interaction Between Magnesium and Neostigmine or Sugammadex for the Reversal of a Rocuronium-induced Neuromuscular Block

First received on December 26, 2017. Last updated on May 8, 2018.

Purpose

Magnesium sulphate is regularly used in perioperative medicine. During and after general anesthesia, it enhances the effect of muscle relaxants because it reduces the liberation of acetylcholine at the neuromuscular junction. When administered immediately after spontaneous recovery of a neuromuscular block (NMB), magnesium may cause a recurrence of NMB and compromise patient safety. Rocuronium is a neuromuscular blocking agent which is frequently used to facilitate intubating and surgical conditions. At the end of the procedure, there are two ways to accelerate the reversal of a neuromuscular block induced by rocuronium: 1. Administration of neostigmine, an anticholinesterase agent and competitive antagonist; 2. Administration of sugammadex, a γ-cyclodextrin compound and specific encapsulator of rocuronium. The study is done in patients receiving rocuronium and either neostigmine or sugammadex for reversal of NMB. It is hypothesized that when sugammadex is used as an antagonist of a rocuronium-induced NMB, it prevents the reappearance of NMB when magnesium is injected, because sugammadex should inactivate all remaining rocuronium molecules and restore neuromuscular reserve of the neuromuscular junctions. Further more it is hypothesized that reversal with neostigmine will not prevent a magnesium-induced recurrence of NMB to the same extent. The primary objective of the study is to show that after reversal with sugammadex there is no or only very little re-occurrence of neuromuscular block after a magnesium perfusion. Furthermore we want to show that after reversal with neostigmine there is a re-occurrence of neuromuscular block.

Status	Not yet recruiting
Condition	Neuromuscular Blockade
Phase	Phase 4
Study Type	Interventional
Official Title	Interaction Between Intravenous Magnesium Sulphate and Neostigmine or Sugammadex for the Reversal of a Rocuronium-induced Neuromuscular Block - A Randomized, Double Blinded, Electrophysiological Study

Further study details (as provided by National Institutes of Health Clinical Center (CC))

Enrollment	48
Start Date	July 1, 2018

Detailed Description

Magnesium sulphate ($MgSO_4$) is regularly used in perioperative medicine. For instance, pre-eclampsia and eclampsia have been successfully treated with intravenous magnesium. Also, $MgSO_4$ has been used for the control of life threatening cardiac arrhythmias, bronchial asthma or as an anticonvulsant. Finally, magnesium has been found to alleviate postoperative pain and to exert morphine sparing effect. Magnesium plays a role in nearly every physiological system. In the nervous system, magnesium has a depressant effect related to the inhibition of transmitter release from presynaptic sites by competing with calcium and due to the antagonism at NMDA receptors. The presynaptic inhibition of acetylcholine release at the neuromuscular junction by magnesium has been well described. In addition, an excess of magnesium ions diminishes the depolarizing action of acetylcholine at the end-plate, and depresses the excitability of the muscle fiber membrane. Magnesium per se causes significant neuromuscular blockade (NMB) in high concentrations (≥ 5 mmol L-1). In the presence of curare-like agents, however, very low concentrations of magnesium (≥1 mmol L-1) inhibit neuromuscular transmission since in this case much more acetylcholine is needed to produce a magnitude of depolarization of the end-plate compared with normal conditions. Consequently, magnesium enhances the effect of muscle relaxants during and after general anesthesia. The prolongation of the duration of NMB by magnesium may increase the incidence of a residual postoperative neuromuscular block, and consequently may compromise patient safety. In addition, magnesium, when administered immediately after spontaneous recovery of a NMB, may cause recurrence of the NMB ("recurarisation"). Under clinical conditions this may happen whenever magnesium is used in the immediate postoperative period, for instance, for postoperative pain alleviation or for treatment of postoperative cardiac arrhythmia. It is not known, however, whether pharmacological reversal of a NMB prior to magnesium treatment prevents the recurrence of NMB. Recovery after neostigmine (an anticholinestherase agent) administration was approximately 30% less in patients pretreated with $MgSO_4$ compared with those without $MgSO_4$ pretreatment. Sugammadex, a γ-cyclodextrin compound, is a new reversal agent. It is a specific encapsulator of steroidal muscle relaxants such as rocuronium. We have demonstrated that magnesium pretreatment did not prolong the reversal of deep or moderate rocuronium-induced neuromuscular blockade when standard doses of sugammadex were used for reversal. Sugammadex causes a rapid and complete reversal of the neuromuscular blockade by reducing the action of rocuronium on the prejunctional and postjunctional nicotinic acetylcholine receptors (nAChRs). Unlike neostigmine, sugammadex is efficacious in reversing moderate (2 twitches to train-of-four [TOF] stimulation, TOF-count two [TOFC-2]) and deep (post-tetanic count [PTC] of 1 or 2) rocuronium-induced NMB in doses of 2.0 mg kg-1 and 4.0 mg kg-1, respectively. The suggested cause of return of NMB ("recurarisation") subsequent to magnesium administration is the absence of a functional reserve of the neuromuscular junction (safety margin, 70% of receptor capacity) despite a complete recovery of the TOF ratio and twitch amplitude (T1) (main variables of neuromuscular monitoring). It is important to know that the actually available neuromuscular monitoring methods are insensitive to measure the safety margin of the neuromuscular transmission, thus they cannot provide information about the likelihood of block recurrence. Theoretically, recurrence of a NMB due to clinical doses of magnesium happens only in cases where the safety margin is reduced or abolished by a NMB agent. Therefore, to prevent recurrent muscle weakness ideally all relaxant molecules should be eliminated from the neuromuscular synapse before magnesium

is administered. Pharmacological reversal of NMB reduces neuromuscular receptor occupancy and thereby increases the safety margin. Neostigmine augments the amount of acetylcholine at the neuromuscular junction, which competitively antagonizes the NMB and liberates at least partially the synaptic receptor reserves. However, neostigmine is not reliable to completely re-establish neuromuscular function. When sugammadex is administered, the free rocuronium plasma concentration rapidly declines near to zero (like a washout) and consequently the safety margin isincreased. In this context, one can speculate that sugammadex is an ideal antagonist when magnesium treatment is associated with the use of rocuronium. However, it is still unknown whether the administration of magnesium sulphate immediately after pharmacological reversal of the TOF ratio to a normalized 0.9 value (i.e. adequate reversal) re-induces a clinically relevant NMB. If magnesium is used in the immediate postoperative period, we need to know whether, and how, postoperative muscle paralysis as a consequence of the magnesium treatment can be prevented. The hypothesis of this study is that when sugammadex is used as an antagonist of a rocuronium- induced NMB, the neuromuscular junction will be liberated from almost all rocuronium molecules and no recurrent NMB will occur. Furthermore it is hypothesized that reversal with neostigmine will not prevent to the same extent magnesium-induced recurrence of NMB. In addition, the magnitude and time course of the magnesium induced neuromuscular block will be measured.

Eligibility

Minimum Age Eligible for Study:	18 Years
Maximum Age Eligible for Study:	65 Years
Genders Eligible for Study:	All

Criteria

Inclusion criteria: - Patients, age ≥18 to 65 years - American Society of Anesthesiology [ASA] status I or II. - Patient is able to read and understand the information sheet and to sign and date the consent form. - Patient scheduled of elective surgery lasting ≥100 minutes. - Women on the pill should be advised to follow the missed dose advice in the product information. - Women using non-oral hormonal contraceptives, such as depot formulations, should be advised to use additional contraception for the next seven days. Exclusion criteria: - A history of allergy or hypersensitivity to rocuronium, glycopyrronium bromide, neostigmine methylsulfate, sugammadex, or magnesium sulphate - Neuromuscular disease receiving medications known to influence neuromuscular function (for instance, aminoglycosides or phenytoine) - Preoperative medications known to influence neuromuscular function (for instance aminoglycosides, phenytoin, lidocaine) - Patients under toremifene, flucloxacillin and fusidic acid treatment (interaction with sugammadex cannot not be excluded) - Electrolyte abnormalities (for instance, hypermagnesemia) - Atrioventricular heart block - Patients with magnesium treatment within 3 days before study inclusion - Patients with a body mass index <19 or >30 kg/m2 - Patient having participated in any clinical trial within 30 days, inclusive, of signing the informed consent form of the current trial. - Patients undergoing interventions that need a continuous deep NMB (for surgical reasons). - Pregnant or breast feeding women

Contacts and Locations

Please refer to this study by its ClinicalTrials.gov identifier: NCT03497923

Locations

University Hospital of Geneva, Anesthesia Department

Status:	Not yet recruiting
Facility:	Geneva, Canton Of Geneva, 1211, Switzerland

Hôpital du Valais

Status:	Not yet recruiting
Facility:	Sion, 1951, Switzerland

Sponsors and Collaborators

Christoph Czarnetzki

More Information

Other Publications

First Received:	December 26, 2017
Last Updated:	May 8, 2018
ClinicalTrials.gov Identifier:	NCT03497923

ClinicalTrials.gov processed this data on May 16, 2018 Link to the current ClinicalTrials.gov record. (https://clinicaltrials.gov/show/NCT03497923)