Protocol: Sugammadex Titration for Reversal of Rocuronium or Vecuronium

Principal Investigator: Andrew Bowdle MD, PhD, FASE

ClinicalTrials.gov number: NCT05246397

Applicable date: 4/22/2022

Background:
Neuromuscular blocking drugs are used frequently during general anesthesia. The effects of neuromuscular blocking drugs are measured using a twitch monitor, that stimulates the ulnar nerve and measures the evoked response of the adductor pollicis muscle (thumb flexion), or other intrinsic hand muscle. When a series of 4 twitches is administered, the ratio of the first to the fourth twitch (train-of-four ratio) may be used to gauge the degree of muscle relaxation. A train-of-four ratio of 0.9 or greater is considered to represent adequate recovery from neuromuscular blockade. At the end of surgery, antagonists of neuromuscular blockade are commonly administered to reverse any remaining muscle relaxation. Sugammadex is a highly effective reversal agent of the aminosteroid neuromuscular blockings drugs rocuronium and vecuronium, which are the most commonly used neuromuscular blocking drugs. The dose-response relationship for sugammadex has never been completely determined. The dose of sugammadex depends upon the degree of neuromuscular blockade. When at least 1 twitch of the train-of-four is present, the recommended dose of sugammadex is 2 mg/kg. When there are no twitches of the train-of-four present, but at least 1 count of the post tetanic count is present, the recommended dose of sugammadex is 4 mg/kg. However, in several dose ranging studies of sugammadex, and in using sugammadex clinically, we and others have determined that smaller doses of sugammadex, often much less than 2 mg/kg, may be effective producing a train-of-four ratio of 0.9 or greater. Sugammadex binds (encapsulates) aminosteroid neuromuscular blocking drugs tightly and the sugammadex-aminosteroid complex is subsequently cleared by the kidney. Therefore we do not expect that recurrence of neuromuscular blockade would occur, even after small doses of sugammadex, as long as the dose of sugammadex is adequate to produce a train-of-four ratio of 0.9. Additional studies are needed to determine the dose-response for sugammadex and to confirm that recurrence of neuromuscular blockade does not occur after small doses of sugammadex. The purpose of the proposed study is to test the hypothesis that when sugammadex is titrated in 50 mg increments until the train-of-four ratio is 0.9 or greater, that this train-of-four ratio is maintained and there is no recurrence of neuromuscular blockade.

Objectives:
The hypothesis is that when sugammadex is titrated in 50 mg increments until a train-of-four ratio of at least 0.9 is reached, that the train-four-ratio will remain at least 0.9 for 6 hours or until extubation, whichever comes first.

Study design:
Cardiac surgery patients will receive sugammadex in 50 mg increments at the end of surgery, until the train-of-four ratio is at least 0.9 and the train-of-four ratio will be measured hourly in the ICU for 6 hours or until extubation, whichever comes first.

Participants:
Cardiac surgery patients >18 years of age who will routinely remain intubated following surgery with planned admission to the intensive care unit

Inclusion criteria:
Cardiac surgery patients >18 years of age who will routinely remain intubated following surgery with planned admission to the intensive care unit

Exclusion criteria:
Allergy or other contraindication to the use of sugammadex

Recruiting and screening:
An investigator or research assistant will review the electronic procedure schedule and identify potential subjects. Either a research assistant or investigator will approach potential subjects to obtain written consent on the day of the procedure in the pre-operative area prior to any sedation. Alternatively, patients may be contacted by phone to assess their potential interest in participation, with completion of the written consent process in the pre-operative area on the day of surgery, prior to any sedation.

Study procedures:
1. Standard clinical procedure for monitoring and reversal of neuromuscular blockade—Neuromuscular blockade is monitored with EMG-based quantitative twitch monitoring (TwitchView). At the end of surgery, sugammadex is administered to reverse neuromuscular blockade, as defined by a train-of-four ratio of 0.9 or greater. The patient is transported asleep, intubated and ventilated to the intensive care unit where the train-of-four ratio of 0.9 or greater is confirmed on arrival by the respiratory therapist.
2. Study procedure—Instead of administering a standard dose of sugammadex 2 mg/kg or 4 mg/kg, sugammadex will be titrated in 50 mg increments every 5 minutes until a train-of-four ratio of 0.9 or greater is reached. Train-of-four ratio will be measured on arrival in the intensive care unit and then hourly for 6 hours or until extubation if extubation occurs in <6 hours. If the train-of-four ratio is less than 0.9 at any time, additional sugammadex will be administered until the train-of-four ratio is 0.9 or greater. The twitch monitoring results in the operating room just prior to reversal, following reversal and hourly in the intensive care unit will be recorded, along with sugammadex doses. The total dose of rocuronium or vecuronium and the time period of neuromuscular blocking drug will also be recorded. Data will either be recorded in real time by study assistants or retrieved from the electronic medical record. The patient's age, gender, and weight will be recorded. Data will be obtained by study assistants or from the electornic medical record.

Data variables:
The twitch monitoring results in the operating room just prior to reversal, following reversal and hourly in the intensive care unit will be recorded, along with sugammadex doses. The total dose of rocuronium or vecuronium and the time period of neuromuscular blocking drug administration will also be recorded. Data will either be recorded in real time by study assistants or retrieved from the electronic medical record. Data variables: date of procedure, sex, age, weight, height, neuromuscular blocking drug data (dose and time), sugammadex dosing data (dose and time) and twitch monitoring data (prior to, during and after sugammadex administration).

Consent process:
An investigator or research assistant will approach subjects on the day of the procedure, but before any sedation by the anesthesia providers in the pre-operative area. The consent information will be discussed in a private room with heavy curtains and with only the subject and principal investigator present. There is minimal risk of auditory privacy loss since the rooms are large and the curtains provide an auditory barrier. These rooms are routinely used by operating room providers (proceduralists, anesthesiologists, and nursing staff) to obtain consent and interview patients about their medical history. The subjects will hear a presentation of the study that will be supported by photos of twitch monitoring equipment. The subjects will have an opportunity to ask questions. The subjects will understand that they will undergo reversal of neuromuscular blockade and twitch monitoring routinely whether or not they participate in the study. If they participate in the study they will additionally undergo titration of sugammadex and additional twitch monitoring in the ICU for up to 6 hours. After the risks and benefits of participation in this study are explained in layman's language, the subject will be asked if he/she has any questions or concerns about participating in the study. The point will be

clearly made that this is a voluntary study and that the subjects have the opportunity for not participating. A paper copy of the signed consent form will be provided to subjects for their records.

Anticipated risks:
The risks that are specific to this research are minimal (excluding the risk of anesthesia and cardiac surgery, which are not specific to this research). Patients will receive sugammadex regardless of their participation in this study. By participating in this study, patients may receive a smaller dose of sugammadex than they would otherwise receive. Hypothetically, there may be a small chance that a smaller dose of sugammadex could result in a recurrence of neuromuscular blockade. This is mitigated by the fact that the patients will be intubated and ventilated postoperatively, which is routine care following cardiac surgery, thus any recurrence of neuromuscular blockade would not be harmful. If there is any recurrence of neuromuscular blockade, this will be detected by twitch monitoring and additional sugammadex will be administered. The patients participating in this study will not be under anesthesia in the operating room or intensive care unit for a longer time than patients not participating in this study.

Data and safety monitoring:
The PI reviews serious adverse events in real time. The PI will monitor the study and ensure that protocol deviations, AEs, and SAEs are reported to the IRB according to HSD and IRB reporting requirements. For this study, the following standard AE definitions are used:
Adverse event: Any event that requires administration of sugammadex after the patient leaves the operating room, prior to extubation.
Not related: The AE is clearly not related to the study procedures (i.e., another cause of the event is most plausible and/or a clinically plausible temporal sequence is inconsistent with the onset of the event).
Possibly related: An event that follows a reasonable temporal sequence from the initiation of study procedures,
but that could readily have been produced by a number of other factors.
Related: The AE is clearly related to the study procedures.

Statistical analysis:
Sample size is based on previous sugammadex dose-finding studies. The sample size in this study is similar to the largest previous sugammadex dose-finding studies. Descriptive statistics will be presented as number (%) for categorical variables or mean ± standard deviation (SD) for continuous variables. Outcome variables (sugammadex dose) will be compared among twitch response groups using two-sample Student's *t* test with the assumption of unequal variance (Satterthwaite's degrees of freedom), ANOVA, two-sample test of proportions, Wilcoxon rank sum test and Pearson's Chi-squared test as appropriate. All P values will be 2-sided, and statistical significance will be defined as a P value of < 0.05. All statistical analyses will be performed with STATA 11.0 (Stata Corp LP, College Station, TX). Patient and procedure characteristics will be analyzed with R 4.2.1s (R Foundation for Statistical Computing, Vienna, Austria).