# Study Protocol

**Title**

Pharmacokinetic profile and breastmilk excretion of sugammadex in pregnant women

**Short title**

Sugammadex in pregnant women

**Principal Investigators**

**Dr Anthony Hodge** BAppSc (Medical Science), MBBS, FANZCA

Staff Specialist Anaesthetist, Royal Brisbane and Women’s Hospital

Associate Lecturer, University of Queensland

**Co-investigators**

**Professor Jason Roberts** BPharm (Hons), PhD, BAppSc, FSHP

Consultant Clinical Pharmacist, Royal Brisbane and Women’s Hospital

NHMRC Practitioner Fellow, Burns, Trauma and Critical Research Centre, University of Queensland

Professor of Medicine, School of Medicine, University of Queensland

Honorary Professor, Institute of Translational Medicine, The University of Liverpool and The University of South Australia

**Associate Professor Victoria Eley** BSc, MBBS (Hons), PhD, FANZCA

Staff Specialist Anaesthetist, Royal Brisbane and Women’s Hospital

Associate Professor, University of Queensland

**Dr Steven C Wallis** BSc (Hons), PhD

Head of Bioanalysis

UQ Centre for Clinical Research, University of Queensland

**Dr Angela Tognolini** BSc (Hons), MBBS, GradCertClinEdu, FANZCA

Staff Specialist Anaesthetist, Royal Brisbane and Women’s Hospital

Associate Lecturer, University of Queensland

# Summary

General anaesthesia with muscle paralysis remains an essential anaesthetic technique used for pregnant women delivering by caesarean section. The use of rocuronium-induced paralysis with reversal by a new agent, sugammadex, is increasingly used in obstetric anaesthesia. There is little knowledge of the pharmacokinetic profile of sugammadex in pregnant women and no human data on the excretion of this drug in human breastmilk. Pregnancy is known to alter the pharmacokinetics of many drugs and anaesthetists are required to advise women on the amount of drug transferred into their breastmilk. In this study we will describe the pharmacokinetic profile of sugammadex and the amount excreted in breastmilk, in pregnant women undergoing elective caesarean section under general anaesthesia.

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# Introduction

In Western countries general anaesthesia remains the anaesthetic technique of choice for a small percentage of pregnant women. The most common reason for caesarean delivery via general anaesthesia is the requirement for urgent delivery when the mother or fetus is compromised.[1] General anaesthesia remains the technique of choice in elective caesarean section, when there is abnormal placentation, contraindications to neuraxial anaesthesia, spinal abnormalities, inadequate or failed regional attempts and maternal refusal of neuraxial anaesthesia. In Australia approximately 6.1% of all caesarean sections are undertaken under general anaesthesia. [2]

Traditionally suxamethonium has been the muscle relaxant of choice for caesarean section. However this has been challenged over the past 15 years. More recently, the combination “rocuronium-sugammadex” is increasingly used. This combination may cause less oxygen consumption (and less desaturation) than suxamethonium and causes less muscle pain following anaesthesia.[3] Rocuronium-sugammadex is acknowledged by internationally-respected guidelines as suitable drugs for airway management in obstetric care.[4] The administration of rocuronium at a dose of 1.2 mg kg-1 achieves adequate intubating conditions within times frames similar to suxamethonium 1.5mg kg-1. Recent studies have demonstrated rocuronium to be non-inferior to suxamethonium for time to tracheal intubation and provides superior surgical conditions for fetal delivery leading to a shorter incision-to-delivery interval.[5, 6]

The duration of action of rocuronium administered at these doses had historically precluded its use at caesarean section due to prolonged neuromuscular blockade (NMB) for a relatively short surgery. The combination rocuronium-neostigmine (neostigmine is a traditional reversal agent) cannot be used to reverse high doses of non-depolarising muscle relaxants in a short timeframe. The rocuronium-neostigmine combination is also limited by the cholinergic side effects such as bradycardia, bronchospasm and post-operative nausea.[7]

Sugammadex works in a completely different way to neostigmine. It is a modified cyclodextrin designed to encapsulate aminosteroid nondepolarizing muscle relaxing agents rocuronium and vecuronium. A meta-analysis by Carron et al found that sugammadex was superior to its alternative, neostigmine, with faster and more complete recovery of muscle strength.[8] Sugammadex also provides rapid and complete reversal of muscle paralysis in emergency situations (for example can’t intubate, can’t oxygenate) when the mother and baby’s lives may be at risk.[9] The benefits of rocuronium-sugammadex have been highlighted in international obstetric airway management guidelines.[10]

Since the regulatory approval of sugammadex in Australia in 2008, its use in clinical practice has steadily increased, as has the number of sugammadex-related publications.[11] The safety, efficacy and pharmacokinetic profile of sugammadex has been reported in a number of patient populations, including the elderly, paediatrics and patients with impaired renal function.[12-15] There are currently no pharmacokinetic studies on the use of sugammadex in the obstetric population. Manufacturer data sheets advise that caution should be exercised when administering sugammadex to pregnant women due to the lack of human data.[16] Despite this, anaesthetists are using sugammdex due to its superior ability to reverse muscle paralysis.

This study aims to assess the impact of pregnancy on the pharmacokinetic profile of intravenous sugammadex and to determine the amount excreted in breastmilk. We will undertake the study in women requiring general anaesthesia for their elective caesarean section.

# Objectives

1. To describe the pharmacokinetics of sugammadex in obstetric patients
2. To perform Monte Carlo dosing simulations using the population model to define optimized dosing regimens for sugammadex in obstetric patients
3. To utilize the results to implement guidelines for the dosing of sugammadex in patients presenting for caesarean section under general anaesthesia
4. To determine the amount of sugammadex excreted in breastmilk

# Study Design

An open-labelled plasma pharmacokinetic study examining the pharmacokinetics of a single bolus intravenous (IV) dose of sugammadex in women undergoing elective caesarean section under general anaesthesia at the Royal Brisbane and Women’s Hospital (RBWH). We will also determine the amount excreted in breastmilk.

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## 4.1 Participants

Potential participants will be identified in the pre-anaesthesia clinic, following their assessment by the anaesthetist. This clinic occurs at least one day prior to the planned caesarean section and at this clinic it is determined if a general anaesthetic is to be the first plan for anaesthesia technique. After their clinic appointment they will be approached in person by a Research Nurse (ReN) who is independent of the clinical team. The ReN will explain the study and provide an information and consent form for the participant to read and they will answer any questions. Participants will be reassured that their participation is voluntary and if they do not wish to participate, their care will not be affected. The well-being of the mother and baby will be paramount at all times. Sometimes women leave the antenatal clinic unexpectedly (for example, for appointments with other health care providers). In this situation, the ReN will contact them by phone and describe the study. In all cases written and informed consent will be obtained and confirmed again on the morning of surgery.

All participants will be offered ongoing support on the day of caesarean delivery by a dedicated research nurse who will be present to facilitate sampling and to answer questions about the research. Participants will be reassured that they can withdraw from the research project at any time prior to their anaesthetic or at any time in the post-operative period.

***Inclusion criteria:***

* Pregnant women aged > 18 years and < 50 years
* Scheduled for elective caesarean section under general anaesthesia
* Informed consent by patient to participate in study and to store specimens for immediate and future analysis.

***Exclusion criteria:***

* Known or suspected allergy to sugammadex (urticaria, anaphylaxis, other systemic consequences)
* Known or suspected allergy to rocuronium
* Renal impairment – serum creatinine > 70 µmol.L-1[17]
* Patients with fulminant hepatic failure – confirmed by the presence of hepatic encephalopathy, coagulopathy in the presence of liver enzyme derangement or profound hypoglycaemia[18]
* Patients receiving fusidic acid, toremifene and/or flucloxacillin, as these drugs have the potential to displace rocuronium from the sugammadex/rocuronium complex[16]

## 4.2 Methods

Anaesthesia care will be undertaken according to ANZCA guidelines and under the direction of the treating anaesthetist, who is independent of the study team. Intravenous access will be obtained by the anaesthetic team, for use by the anaesthetist (administration of medications and fluid). A second cannula will be inserted, preferably in the anterior cubital fossa of the contralateral arm, which will be used for sampling only (after discarding the first 5 ml of blood at each sampling time point). Locations other than the anterior cubital fossa will also be suitable for sampling provided they are not in close proximity to the administration cannula.

Anaesthesia will be induced intravenously according to the preference of the treating anaesthetist. After the hypnotic agent, an IV bolus dose of rocuronium 1-1.2 mg/kgadjusted for lean body weight will be administered for rapid sequence induction. Following intubation, neuromuscular monitoring will be performed at the adductor pollicis muscle with acceleromyography. This monitoring is standard of care when using muscle paralysis during anaesthesia. Monitoring will be done using the Stimpod NMS450 (Xavant Technology, Pretoria, South Africa). Maintenance of anaesthesia will be at the discretion of the attending anaesthetist. Additional doses of muscle relaxant may be given throughout the case to facilitate optimal surgical conditions and this information will be documented.

At the completion of surgery, sugammadex will be administered for reversal at doses determined by the depth of neuromuscular block and according to the product information: 2 mg kg-1 for moderate neuromuscular block (defined by the appearance of two twitches on train of four) and 4 mg kg-1 for deep neuromuscular block (defined as the appearance of two twitches with post-tetanic count) dosed for total body weight. Following administration of sugammadex, a train of four ratio (TOFR) will be performed at 20 second intervals until a TOFR of >0.9 is observed.

Dr Hodge, Dr Eley and Dr Tognolini are anaesthetists who will potentially be rostered to provide anaesthesia care for a research patient. In this circumstance recruitment and sample collection will still be performed by the independent research nurses. Usually alternate anaesthetic care can be arranged to avoid the researchers providing direct care to the research participant.

***Blood and urine sampling***

A baseline blood sample (t = 0 minutes) will be obtained prior to induction of anaesthesia and at 5, 10, 15, 20, 30, 60 minutes after dosing with sugammadex. A further sample will be taken at 6 hours post sugammadex administration with a final sample at 24 hours that will be taken during routine post caesarean section phlebotomy on day one post-operatively. Blood samples will be stored on ice and within 2 hours spun at 3000 rpm for 10 minutes, the plasma aspirated and stored at -80oC until assayed by validated Liquid Chromatography-Mass Spectrometry (LC-MS). Urine will be collected via the indwelling catheter from the time of sugammadex administration until 6 hours post sugammadex dose. The collected urine will be stored at -80oC until assayed by LCMS.

***Breastmilk sampling***

During recovery from anaesthesia, it is usual practice to initiate breastfeeding as soon as possible. The Research Nurse with the assistance of the attending midwife will assist the participant in providing a sample of breastmilk, 0.2-0.4 mL in a sterile syringe in the post anaesthetic care unit one hour following sugammadex administration. A further 0.2-0.4 mL sample of breast milk will be collected at six hours post-operatively. After collection, the breast milk samples will be stored at -80 oC until assayed by LCMS.

Data from the plasma and breast milk samples will be used to calculate the milk-plasma (M/P) ratio as follows: M/P = sugammadex concentration in the colostrum/sugammadex concentration in plasma. Relative infant dose will be calculated as follows: RID (%) = absolute infant dose (mg/kg/day)/maternal dose (mg/kg/day) x 100.[19]

## 4.3 Data Collection

The following parameters will be recorded:

1. Patient Demographics – maternal age, parity, gestational age at delivery, singleton or twins/triplet pregnancy, height, weight (within 2 weeks of surgery), BMI (based on the weight within 2 weeks), comorbidities, pregnancy-related conditions, study number, medical record number
2. Pre-operative blood tests (these are collected routinely): haemoglobin included as part of: Full blood count. Non-routine blood tests: Serum biochemistry, Liver function tests
3. Post-operative blood tests: haemoglobin
4. Procedure details – type of caesarean section (lower uterine segment or classical, indication for caesarean section, indication for general anaesthesia, operative time (knife-to-skin to dressings), time to delivery of baby (induction of anaesthesia to delivery of the baby),
5. Anaesthesia details: total volume and type of intravenous fluids administered (mL), urine output (from time of catheter insertion until removal post-operatively, or 24 hours post catheter insertion), estimated blood loss, with pre and postoperative haemoglobin and other medications administered for anaesthesia and analgesia intra-operatively.

* Date and time of rocuronium dosing and the dose in mg/kg
* Date and time of sugammadex dosing and the dose in mg/kg
* Results of neuromuscular monitoring (calibration and subsequent testing prior to and following reversal)
* Any adverse events or difficulties definitively or suspected to be associated with the sugammadex administration
* Post Anaesthetic Care Unit (PACU) data – train of four ratio, time in PACU, any airway or ventilation-related adverse events, complications post-operatively requiring airway support, supplemental oxygen or re-intubation due to patient or surgical factors. Type and dose of muscle relaxant used for subsequent intubation if required.

## 4.4 Pharmacokinetic Analysis

Individual concentration-time curves for sugammadex will be created for each participant. The intended sample size is 15 participants. Population pharmacokinetic models will be developed from the samples obtained from the 15 individuals and from the collected data, using the modelling software PMetrics®. The pharmacometrics team at the UQ Centre for Clinical Research, will perform regression analysis to statistically validate these models, which can then be used to perform Monte Carlo dosing simulations with PMetrics®, which essentially creates a simulated patient population of 1000 patients based on the different pharmacokinetics in the included patients, to determine whether current dosing regimens achieve adequate drug concentrations, or which optimised dosing regimens should be trialled for efficacy in future studies.

If missing data occurs in this study, from a pharmacokinetic perspective this can be accounted for using the population pharmacokinetic analysis method we intend to use. Because of the deliberate richness of sampling we have proposed, we do not envisage that missing 1 or 2 samples in a selection of our patients would at all be problematic and the conclusion of our analysis would still be as robust.

**Data management and storage**

Each patient enrolled in the trial will be assigned an identification number. Data will remain re-identifiable for the duration of the study however when data collection is complete, it will be de-identified by the use of labelling with the participant ID number only, that is no identifying information will be recorded long-term for this research. The data collection tool will be via a REDCAP database. The master list allowing re-identification of patients will only be available to the principal researchers and stored on encrypted computers in a site restricted to research staff. Electronic data will be stored on password protected computers within the locked anaesthetic department and any hard copies will be stored in the restricted access, locked office of the RBWH anaesthetic research department. Data security will be maintained at all times and destroyed as per protocol after 15 years. Publication or presentation of results will not include any individually identifying information.

## Feasibility

Audit data undertaken at our institution between July 2018 and October 2019 revealed that of 957 elective caesarean sections, 30 (3.1%) were undertaken under general anesthesia. In those cases, the muscle relaxant used for intubation paralysis was rocuronium in 19 (63%) cases and suxamethonium in 11 (37%). This demonstrates that local anaesthetists have adopted rocuronium for use in caesarean section. Importantly, of the cases that used rocuronium for intubation paralysis, 9 (47%) used sugammadex for reversal. This indicates that our local anaesthetists are comfortable using sugammadex in this clinical context and highlights the importance of providing this data. Based on our audit data, for 15 participants, we estimate data collection to be complete within 12 months.

1. **Dissemination**

It is intended that this research will be presented at national and international meetings and published in a peer-reviewed journal.

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