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NEWSLETTER
THE OFFICIAL JOURNAL OF THE ANESTHESIA PATIENT SAFETY FOUNDATION

CITATION: Yang K, Ratto C, Szokol J, Osumi A. Safety of sugammadex in pregnancy, pediatrics, and renal failure. *APSF Newsletter.* 2025:1,6-9.

Safety of Sugammadex in Pregnancy, Pediatrics, and Renal Failure

by Kevin Yang, BS; Christina Ratto, MD; Joseph Szokol, MD; and Ashley Osumi, MD

In 2023, the American Society of Anesthesiologists published practice guidelines for the monitoring and antagonism of neuromuscular blockade.[1] The guidelines recommended quantitative monitoring over qualitative assessment to avoid residual blockade. The guidelines also called for the use of sugammadex over neostigmine at different depths of blockade. While these guidelines provide a framework for general practice, they do not address specific considerations for special patient populations, such as those with renal failure, pregnant women, and pediatric patients.

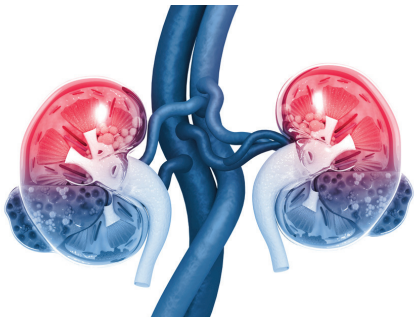
SAFETY OF SUGAMMADEX IN RENAL FAILURE

Sugammadex is primarily excreted by the kidneys and poses challenges in patients with severe renal impairment due to the risk of recurarization (Figure 1, page 7).[2] The recurarization, resulting in potential paralysis or residual weakness, presumably occurs because the circulating rocuronium-sugammadex complexes can disassociate. In patients with normal renal function, the elimination half-life of sugammadex is about 2 hours and the estimated plasma clearance is about 88 mL/min. Studies show over 90% of the dose is excreted within 24 hours, with 96% excreted unchanged in urine. However, in renal impairment, the half-life extends to 4, 6, and 19 hours in mild, moderate, and severe cases, respectively.[2]

The rocuronium-sugammadex complex is highly stable due to intermolecular (van der Waals) forces, thermodynamic (hydrogen) bonds, and hydrophobic interactions.[3] For every 25 million sugammadex-rocuronium complexes, only 1 complex dissociates. The complex is water-soluble and excreted in the urine in patients with normal renal function. The complex is also removed during dialysis with a high-flux filter.[4]

In patients not getting dialysis, there is a theoretical concern in anuric patients that the rocuronium-sugammadex complex may persist in the plasma longer leading to higher rates of disassociation.

In clinical practice, managing patients with renal failure who necessitate paralysis poses a dilemma. The anesthesia professional can either administer neuromuscular agents and then wait until recovery of function or opt for alternative agents like a benzylisoquinolinium



such as cisatracurium, which is not reversible by sugammadex. A recent prospective, randomized, blinded, controlled trial addressed this, comparing sugammadex and neostigmine for reversing moderate blockade in renally impaired patients.[5] The study demonstrated sugammadex's superiority, achieving Train-of-Four Ratio (TOFR) >90% significantly faster (3.5±1.6 min) compared to neostigmine (14.8 ± 6.1 min), without major adverse events. This suggests that the use of sugammadex to reverse moderate blockade is safe and faster than a combination of neostigmine/cisatracurium in renally impaired patients. Ideally, a quantitative neuromuscular monitor should be used to assess adequacy of reversal in these patients.

SAFETY OF SUGAMMADEX IN PREGNANCY

The use of sugammadex in pregnancy poses a significant dilemma for anesthesia professionals due to the lack of substantial evidence indicating its clinical dangers in this patient population. Despite the absence of definitive data demonstrating harm, the Society for Obstetric Anesthesia and Perinatology (SOAP) guidelines restrict its use, leaving clinicians with limited options. This cautious stance by SOAP reflects the broader challenge in medical practice where the scarcity of conclusive research data on drug safety in pregnancy often results in conservative recommendations, potentially impacting the optimal management of pregnant patients requiring neuromuscular blockade reversal. In this section, we evaluate the current evidence on the safety, efficacy, and side effects of sugammadex in the context of pregnancy.

Many of the potential pregnancy-related side effects of sugammadex stem from its potential to bind progesterone. The initial manufacturer's model suggested potential binding to progestin, prompting speculation about similar interactions with progesterone.[6] Subsequent *in vitro* studies have supported that sugammadex can in fact bind to progesterone. In pregnant patients undergoing nonobstetric surgery, there is concern that sugammadex might decrease progesterone levels which are crucial for maintaining pregnancy. However, the current preclinical evidence on this matter is inconclusive. A single preclinical study found that administering high-dose sugammadex (30 mg/kg) to first-trimester pregnant rats did not reduce endogenous progesterone levels or affect live birth or stillbirth rates.[7,8] Conversely, a subsequent study in which pregnant rabbits underwent general anesthesia including paralysis reversal with sugammadex showed significant decreases in progesterone levels; however, all rabbit pregnancies were successful, without early births or stillbirths.[8] The only currently published human evidence is a single case report that describes a pregnant patient who underwent surgery for ovarian torsion who did not experience any pregnancy-related side effects following sugammadex administration.[9] Large retrospective studies and a registry in which providers report on the use of sugammadex in pregnant patients could help better elucidate the effect of sugammadex on pregnancy progression.[6]

While neuraxial anesthesia is preferred in the setting of obstetrics, general anesthesia is necessary under certain conditions. As such, there has been investigation on how sugammadex may effect obstetric outcomes. The possible sugammadex binding of progesterone is again of concern in this context, as decreased progesterone is associated with preterm labor and preterm premature rupture of membranes.[6] A case series involving 25 pregnant women who received sugammadex during the antenatal period identified no obstetric complications directly attributable to sugammadex.[7,10] The authors attribute the lack of complications to minimal placental transfer of sugammadex and its high affinity for rocuronium, which may prevent significant sequestration of progesterone. Given sugammadex's elimination half-life of about 2 hours, most of the medication should be cleared from the bloodstream within 48 hours, implying that any potential effects on

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progesterone binding would manifest shortly within that period.

In cesarean deliveries requiring general anesthesia, sugammadex has been shown to be effective and safe for reversing rocuronium-induced neuromuscular blockade at the end of cesarean deliveries, even in cases of profound neuromuscular block.[7,8,11] However, there is limited evidence on the effectiveness of sugammadex for rescue reversal in cannot-intubate/cannot-ventilate scenarios after rapid sequence induction.[7] Despite this, guidelines recommend considering high-dose sugammadex for immediate reversal in such emergencies because the sequelae of severe hypoxia could be more detrimental than the potential risks that may arise from sugammadex exposure.[8]

Concerns about sugammadex teratogenicity arise from cell culture studies showing it may promote neuronal apoptosis due to oxidative stress,[8] but this effect was not seen in mice with mature blood-brain barriers.[7,8] Combined with sevoflurane, increased neuronal apoptosis occurred in mice.[7] Preclinical studies found no adverse effects in pregnant rats, but high doses in New Zealand white rabbits caused decreased fetal body weight and bone ossification issues, with no malformations observed.[8] No evidence exists regarding these effects in humans.

Just as the large and polarized sugammadex molecules may limit the drug's ability to cross the blood-brain barrier, these biochemical properties are also thought to limit its excretion into breast milk.[8] Sugammadex passage into breast milk is of concern because the infant's immature metabolism and renal function may delay clearance of the agent. An unpublished preclinical study demonstrated peak sugammadex levels in rat milk 30 minutes post-administration without adverse effects on offspring.[7] However, there is no evidence regarding sugammadex in human breast milk.[7] Given the lack of human evidence, breastfeeding immediately after received sugammadex is discouraged due to peak concentrations of sugammadex occurring around one hour postdelivery and potential increased passage into breast milk during the early postpartum period.[8]

While sugammadex offers critical benefits in pregnancy for rapid reversal of neuromuscular blockade, uncertainties persist regarding its interaction with progesterone, teratogenic potential, and safety during breastfeeding. Robust clinical data are needed to delineate these risks comprehensively and guide safe practices in obstetric and nonobstetric settings where its use is necessary.

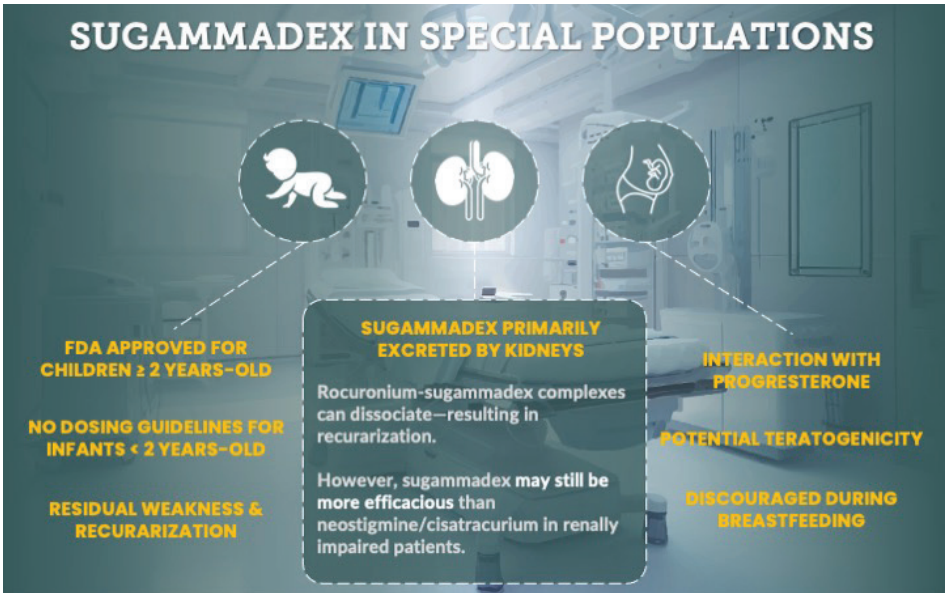

Figure 1: Use of sugammadex in special populations.

SAFETY OF SUGAMMADEX IN THE PEDIATRIC PATIENT

When sugammadex was introduced to the US market, FDA approval was only for use in adults. The Bridion® package insert (Merck, Rahway, NJ) outlined that the safety and effectiveness of the drug had yet to be established in patients under 17 years of age.[2] Compared to adult patients, pharmacokinetics and pharmacodynamic profiles vary by age group, and a high age-dependent variability has been observed in pediatric patients in response to muscle relaxants and neuromuscular blockade reversal agents.[12] Numerous studies and case reports have since been published, and in 2021, an updated package insert was released with FDA approval for use in patients 2 years and older. Sugammadex provides safe, effective, and predictable reversal of neuromuscular blockade in pediatrics, revolutionizing care and improving outcomes in pediatric surgical settings. This section will focus on sugammadex in different pediatric age groups, recurarization, adverse events, and use in specific pediatric populations.

SUGAMMADEX USAGE BY AGE GROUP

Children aged 2–17

Sugammadex has been FDA-approved for use in children 2 years and older with the same dosing parameters as adults for moderate and deep blockade. The dose of 16 mg/kg for immediate reversal in pediatric patients has not been studied and is not FDA-approved for use.[2] Compared with neostigmine, reversal of moderate blockade with 2 mg/kg sugammadex occurred significantly faster.[13] Within 3 minutes, over 90% of the pediatric population had a TOFR > 0.9. The time to reversal of deep neuromuscular blockade with 4 mg/kg was consistent with results found in the adult population.[13] Sugammadex use was associated with a significantly shorter duration from the administration of reversal agents to TOFR > 0.9 compared to acetylcholinesterase inhibitors. There is also an association with shorter interval from reversal of neuromuscular blockade to extubation compared to acetylcholinesterase inhibitors. These findings demonstrate the superiority of sugammadex for reversing neuromuscular blockade over the conventional drugs such as the acetylcholinesterase inhibitors.[14]

Infants (less than 2 years)

Currently, sugammadex use in infants to children under 2 years of age is considered off-label, as safety and effectiveness data have yet to be clearly established. There still needs to be validated pediatric dosing, and inconsistencies with monitoring have led to a wide range of approaches to the use of sugammadex as a reversal drug. Infants exhibit diverse reactions to neuromuscular blocking agents because of their immature neuromuscular junctions, larger extracellular volume during development, distinct body composition, anatomy, respiratory physiology, and muscle mass, all contributing to varying responses to neuromuscular blocking agents (NMBAs).[15] Additionally, the morphology of acetylcholine receptors differs from that of adults, and neuromuscular transmission is immature in neonates and infants until 2 months of age. Fetal postjunctional receptors are more sensitive to neuromuscular blockers as they have prolonged opening times. Pharmacokinetics are also affected by infants' underdevel-

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Pediatric Patients Receiving Sugammadex Do Not Have a Higher Incidence of Bradycardia Than Those Receiving Neostimine in the Operating Room

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oped hepatic and renal function, which reduces NMB clearance.[16]

In a prospective pilot trial, a sugammadex dose of 2 mg/kg was used in children aged 1–12 months old. Similar time to recovery of TOFR in all age groups was observed with no subsequent TOFR decrease after initial TOFR recovery to 0.9.[17] Redosing occurred in 4.2% of the cases after an initial dose of 3.45 mg/kg in children under 2 years of age. However, in this study, the use of neuromuscular blockade monitoring was inconsistent as only 43.7% of patients received train of four monitoring.[16] Overall, there are no specific dosing guidelines for neonates, and further investigation is needed to determine the appropriate dose of sugammadex in children under 2 years of age.

RESIDUAL WEAKNESS AND RECURARIZATION

Postoperative residual paralysis impacts respiratory function and compromises ventilation, increasing the incidence of critical postoperative respiratory events.[18] The pediatric population is more vulnerable to hypoxemia due to smaller lung volumes, reduced Functional Residual Capacity (FRC), immature respiratory control and high oxygen demand, and postoperative recurrent paralysis "recurarization." While residual weakness and recurarization occur in both adult and pediatric populations, children, particularly infants, have an increased susceptibility to postoperative respiratory complications due to anatomical airway differences when exposed to lingering effects of neuromuscular blocking agents.[15] The overall incidence of residual postoperative weakness has been reported as high as 28.1% in children, which may be due to inappropriate neostigmine use, as it cannot reverse deep neuromuscular block.[15] One of the advantages of sugammadex is the ability to reverse both moderate and profound block, and it has been shown to reduce the risk of residual neuromuscular blockade. Multiple large-scale retrospective and prospective studies reviewed sugammadex use in pediatrics, in which both recurarization was not observed, and additional doses of neuromuscular reversal agents were not required.[13,17] However, case reports have described recurarization events that required additional reversal. In a case series of four pediatric patients with residual weakness or recurarization, three of the patients were under the age of 2. After adequate reversal with sugammadex and extubation was executed, the patients were noted to have a decreased respiratory effort, minimal limb movement, weakness, and cyanosis. In these patients, repeated sugammadex dosing had near-immediate improvement in ventilatory effort and strength. An additional patient, age 11, was also noted to be adequately reversed and required additional sugammadex 50 minutes after the initial dose, followed by improved ventilatory effort and eye-opening.[19] In a different case report describing an eight-month-old with DiGeorge and Truncus Arteriosus, who was adequately reversed using TOF monitoring at the adductor pollicis muscle, the patient required a repeat sugammadex dose 20 minutes after extubation.[20] While uncommon, the need for additional reversal does occur, and close monitoring and awareness during the postoperative period are essential to avoid complications.

ADVERSE EVENTS IN PEDIATRICS

Children can experience adverse events such as recurarization or anaphylaxis. There are considerations specific to the pediatric population. In young children, cardiac output is heart rate-dependent, and dose-dependent bradycardia could have a more clinically significant hemodynamic impact.[21] There was no significant difference between patients receiving sugammadex 2 mg/kg, 4 mg/kg, or neostigmine in the incidence of bradycardia while in the operating room.[13] At the same time, a meta-analysis with trial sequential analysis noted a significantly lower incidence of bradycardia in patients receiving sugammadex compared to acetylcholinesterase inhibitors or placebo in the operating room.[14]

CONCLUSION

The evolving landscape of neuromuscular blockade reversal continues to advance clinical practice, and sugammadex has emerged as a preferred agent in many settings. It has shown efficacy and safety in many different patient populations including those with renal impairment, during pregnancy, and pediatrics. By continuing to expand clinical evidence, anesthesia professionals can optimize patient care and safety in the management of neuromuscular blockade and reversal.

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The authors have no conflicts of interest.

REFERENCES

1. Thilen SR, Weigel WA, Todd MM, et al. 2023 American Society of Anesthesiologists practice guidelines for monitoring and antagonism of neuromuscular blockade: a report by the American Society of Anesthesiologists Task Force on Neuromuscular Blockade. *Anesthesiology.* 2023; 138:13–41. PMID: 36520073.
2. Bridion (sugammadex) [prescribing information]. Rahway, NJ: Merck & Co., Inc.; 2022. https://www.merck.com/product/usa/pi_circulars/b/bridion/bridion_pi.pdf. Accessed December 12, 2024.
3. Bom A, Bradley M, Cameron K, et al. A novel concept of reversing neuromuscular block: chemical encapsulation of rocuronium bromide by a cyclodextrin-based synthetic host. *Angew Chem Int Ed Engl*. 2002;41:266–270. PMID: 12491405.
4. Cammu G, Van Vlem B, van den Heuvel M, et al. Dialysability of sugammadex and its complex with rocuronium in intensive care patients with severe renal impairment. *Br J Anaesth*. 2012;109:382–390. PMID: 22732111.
5. Oh MW, Mohapatra SG, Pak T, et al. Sugammadex versus neostigmine for reversal of neuromuscular blockade in patients with severe renal impairment: a randomized, double-blinded study. *Anesth Analg*. 2024;138:1043–1051. PMID: 38190344.
6. Gaston IN, Lange EMS, Farrer JR, Toledo P. Sugammadex use for reversal in nonobstetric surgery during pregnancy: a reexamination of the evidence. *Anesth Analg*. 2023;136:1217–1219. PMID: 37205805.
7. Richardson MG, Raymond BL. Sugammadex administration in pregnant women and in women of reproductive potential: a narrative review. *Anesth Analg*. 2020;13:1628–1637. PMID: 31283616.
8. Do W, Cho AR. What we need to know and do on sugammadex usage in pregnant and lactating women and those on hormonal contraceptives. *Anesth Pain Med (Seoul)*. 2023;18:114–122. PMID: 37183279.
9. Varela N, Lobato F. Sugammadex and pregnancy, is it safe? *J Clin Anesth*. 2015;27:183–184. PMID: 25516396.
10. Singh S, Klumpner TT, Pancaro C, et al. Sugammadex administration in pregnant women: a case series of maternal and fetal outcomes. *A A Pract*. 2021;15:e01407. PMID: 33626026.
11. Pühringer FK, Kristen P, Rex C. Sugammadex reversal of rocuronium-induced neuromuscular block in Caesarean section patients: a series of seven cases. *Br J Anaesth*. 2010;105:657–660. PMID: 20736231.
12. Won YJ, Lim BG, Lee DK, et al. Sugammadex for reversal of rocuronium-induced neuromuscular blockade in pediatric patients. *Medicine*. 2016;95:e4678. PMID: 27559972.
13. Voss T, Wang A, DeAngelis M, et al. Sugammadex for reversal of neuromuscular blockade in pediatric patients: results from a phase IV randomized study. *Paediatr Anaesth*. 2021; 32:436–445. PMID: 34878707.
14. Lang B, Han L, Zeng L, et al. (2022). Efficacy and safety of sugammadex for neuromuscular blockade reversal

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in pediatric patients: an updated meta-analysis of randomized controlled trials with trial sequential analysis. *BMC Pediatr*. 2022;22:295. PMID: 35590273.

15. Scheffenbichler FT, Rudolph MI, Friedrich S, et al. Effects of high neuromuscular blocking agent dose on post-operative respiratory complications in infants and children. *Acta Anaesthesiol Scand*. 2020;64:156–167. PMID: 31529484.
16. Cates AC, Freundlich RE, Clifton JC, Lorinc AN. Analysis of the factors contributing to residual weakness after sugammadex administration in pediatric patients under 2 years of age. *Paediatr Anaesth*. 2023;34:28–34. PMID: 37792601.
17. Zhang R , Hu J, Li S ,et al. Effects of age on sugammadex reversal of neuromuscular blockade induced by rocuronium in Chinese children: a prospective pilot trial. *BMC Anesthesiol.* 2021;21:248. PMID: 34666673.
18. Tobias JD. Current evidence for the use of sugammadex in children. *Paediatric Anaesthesia*. 2017;27:118–125. PMID: 27859917.
29. Lorinc AN, Lawson KC, Niconchuk JA , et al. Residual weakness and recurarization after sugammadex administration in pediatric patients: a case series. *A A Pract*. 2020;14:e01225. PMID: 32539277.
20. Carollo, DS, White WM. Postoperative recurarization in a pediatric patient after sugammadex reversal of rocuronium-induced neuromuscular blockade: a case report. *A A Pract*. 2019;13:204–205. PMID: 30985317.
21. Gaver, RS, Brenn, BR, Gartley, A, Donahue BS. Retrospective analysis of the safety and efficacy of sugammadex versus neostigmine for the reversal of neuromuscular blockade in children. *Anesth Analg*. 2019; 129:1124–1129. PMID: 31584918.