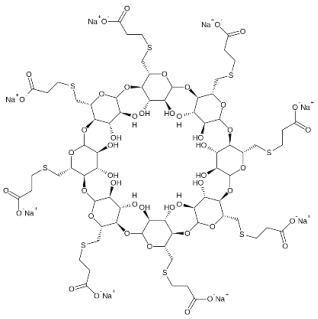
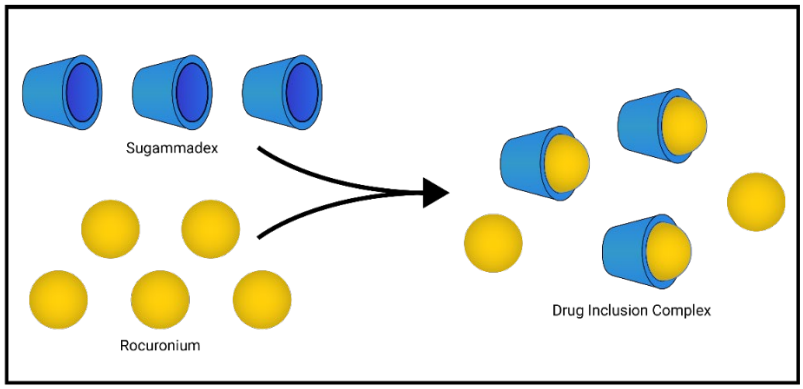
Clinical Pharmacology & Toxicology Pearl of the Week

~ Sugammadex – Pharmacology Considerations ~



Sugammadex is a γ-cyclodextrin containing eight glucose molecules arranged in a ring around a central cavity. Sugammadex is designed to bind amino-steroid neuromuscular blockers (e.g. rocuronium) within their cavity based on ring size and the charge of its side chains. This binding forms a drug inclusion complex which prevents the drug from interacting with receptors. In this way, sugammadex binding to rocuronium produces rapid reversal of rocuronium's paralysis effect. Sugammadex and the drug inclusion complex are then renally cleared.[1]



Clinical Use of Sugammadex:

Sugammadex is used to reverse the neuromuscular blocking effects (i.e. paralysis) of rocuronium. Sugammadex is being introduced in Alberta for **restricted use** in select circumstances. While some have advocated for routine use of sugammadex after surgical procedures to reduce the risk of pneumonia and atelectasis caused by residual respiratory muscle weakness, this is not currently an approved use in Alberta.[2] Instead, sugammadex is indicated in the follow circumstances:

1. Immediate reversal of rocuronium in a life-threatening emergency situation where intubation or oxygenation cannot be achieved by alternative measures (Cannot Intubate Cannot Oxygenate).
2. Patients with a difficult airway to reduce the risk for re-intubation and avoid Cannot Intubate Cannot Oxygenate related morbidity and mortality.

Dosing for emergency situations is **16 mg/kg IV push over 10 seconds** which fully reverses paralysis at standard rocuronium doses. Clinical effect is seen roughly 3 minutes after administration and preparation of the medication is expected to take 2 minutes. Therefore, clinicians should expect at least 5 minutes from the time sugammadex is ordered to reversal of

paralysis and further attempts at intubation or oxygenation, including front of neck access if clinically indicated, should be pursued while sugammadex is being administered.

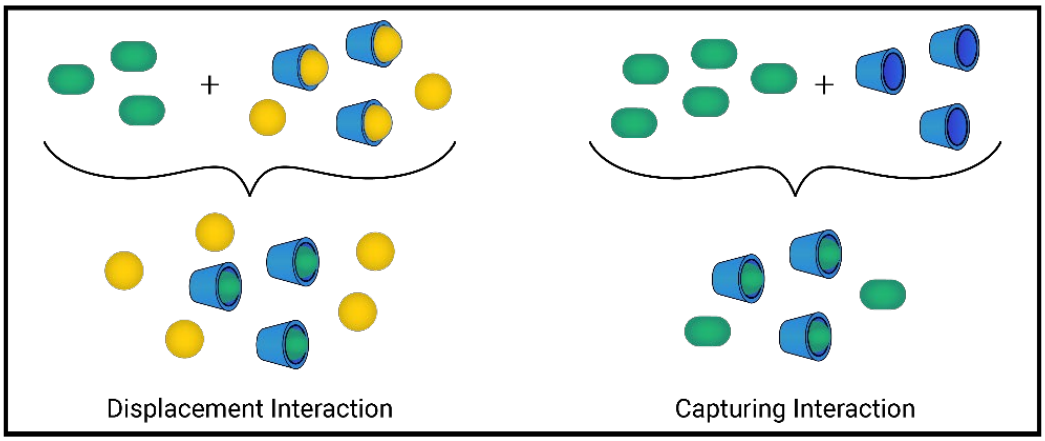
Return of spontaneous respiratory effort due to reversal of paralysis is the primary clinical sign of sugammadex effect. However, it is important to note that sugammadex does not reverse the effects of other sedatives or respiratory suppressants administered during induction of anesthesia.

Pharmacokinetic Interactions:
Cyclodextrin compounds are unique in their drug interaction profile as they do not exert direct physiologic effects (i.e. receptor activation, enzyme inhibition). Instead, their actions are mediated by binding to other xenobiotics and reducing their effect. Conceptually, pharmacokinetic interactions with all cyclodextrins including sugammadex can be categorized as 'displacement interactions' and 'capturing interactions' as outlined below:[3]

Displacement Interactions:
A drug with affinity for sugammadex is administered and displaces rocuronium from sugammadex, increasing the free rocuronium level. This can manifest in two scenarios:

1. If the drug is circulating in the plasma prior to sugammadex administration, higher doses of sugammadex will be required for reversal of paralysis, as part of the sugammadex dose will bind the competing drug instead of rocuronium.
2. If the drug is administered after sugammadex is used to reverse rocuronium, but prior to the rocuronium-sugammadex complex being excreted in the urine (within 7.5 hours), rocuronium can become displaced from the sugammadex ring, resulting in increased free rocuronium level and possible recurrence of paralysis.

Capturing Interactions:
Sugammadex binds to another xenobiotic, decreasing its efficacy. The total plasma level of the drug may be unchanged, but free drug level is reduced.



Clinically Relevant Drug Interactions:

1. Hormonal Contraception:
   Sugammadex has been shown to bind (capture) both estrogen and progesterone, with reductions in progesterone exposure of 34% after a single dose of sugammadex.[3] This is comparable to missing a single dose of oral contraception and is expected to reduce the efficacy of all forms of hormonal contraception including oral contraceptive pills, depot progestin injections, and hormonal intrauterine devices.
   - FDA prescribing information recommends that patients using hormonal contraception who are exposed to sugammadex use barrier contraception for at least 7 days after sugammadex.
   - Multiple studies have shown low rates of patient counselling regarding this interaction and unintended pregnancy has been reported during the same menstrual cycle as sugammadex exposure.[4,5]

2. Selective Estrogen Receptor Modulators:
   - Toremifene has been shown to have very strong binding to sugammadex and reach high enough plasma concentrations to interfere with sugammadex binding to rocuronium (displacement).[3]
   - While **tamoxifen** has not been directly studied, its chemical structure is nearly identical to toremifene and therefore would be expected to have similar risk for displacement.
   - If tamoxifen or toremifene are taken prior to sugammadex administration (i.e. on the day of surgery), the effect of sugammadex may be reduced or delayed and quantitative train-of-four monitoring is recommended during reversal of neuromuscular blockade.
   - If sugammadex has been used to reverse rocuronium, tamoxifen or toremifene should not be administered for at least 8 hours after reversal to ensure the drug inclusion complex has been excreted prior to administering a drug which could displace rocuronium and have the potential to cause recurrence of paralysis.

3. Other Potential Interactions:
   - IV fusidic acid and flucloxacillin have also been predicted to carry a risk of displacement interactions in pharmacokinetic modelling studies.[3] While neither of these medications is routinely used in Canada, administration should follow similar recommendations as toremifene (i.e. avoid for at least 8 hours after sugammadex).
   - Corticosteroids have been shown to have partial binding affinity for sugammadex in pharmacokinetic modelling studies but are not believed to cause significant displacement. Binding was greatest from betamethasone and fludrocortisone.[3] The ability for sugammadex to bind corticosteroids (capture) has not been well studied, but there is the potential to cause a mild reduction in corticosteroid efficacy.

Adverse Effect Profile:

- Cardiovascular: Transient bradycardia has been reported in up to 8% of cases in some series.[6] Most of these studies report no significant blood pressure changes, and no need for intervention with this self-resolving bradycardia. However, third degree AV block and cardiac arrest has been reported in case reports.[7,8] It is recommended that atropine be immediately available when sugammadex is administered.
- Gastrointestinal: Nausea and vomiting following sugammadex administration have been reported.

- Hemostasis: Sugammadex has been shown to transiently increase INR and aPTT in a dose-dependent fashion. The mechanism for this elevation is not understood. However, this has not been shown to correlate with clinically relevant bleeding risk.[9]

Use of Sugammadex in Renal Failure:

As previously mentioned, sugammadex is renally cleared and does not undergo significant hepatic metabolism. This has led to concern that if sugammadex is administered in patients with end-stage renal disease, the sugammadex-rocuronium complex will not be cleared and dissociation of the complex could cause recurrence of paralysis. Many monographs recommend that sugammadex is not used for patients with a CrCl < 30 mL/min or in patients requiring dialysis. However, these concerns are largely unfounded for the following reasons:

1. Binding between rocuronium and sugammadex has not be shown to decrease over time, so rocuronium should stay bound as long as sufficient levels of sugammadex remain.
2. The impact of renal impairment on clearance is greater for sugammadex than rocuronium because rocuronium undergoes biliary excretion and partial hepatic metabolism. Therefore, rocuronium will be excreted before sugammadex levels decrease.
3. Multiple trials have shown no recurrence of neuromuscular blockade after administration of sugammadex to patients with end-stage renal disease.[1]

However, studies have shown that the time to reversal of paralysis with deep neuromuscular blockade is mildly prolonged in patients with end-stage renal disease (5.6 vs. 2.6 minutes). Because of the delayed response and altered dose-response curve, quantitative train-of-four monitoring is recommended if available.[1]

More relevant in patients with end-stage renal disease is the question of how long sugammadex effects may last, making the patient resistant to rocuronium if the require repeat neuromuscular blockade for additional operations. For patients with normal renal function, it is recommended to use an alternative paralytic agent (i.e. succinylcholine or cisatracurium) for at least 24 hours after sugammadex. However, the half-life of sugammadex in end-stage renal failure is > 19 hours which could contribute to reduced rocuronium efficacy for upwards of 4 days. Therefore, an alternative paralytic agent should be considered for at least 4 days if sugammadex is used in end-stage renal failure. Alternatively, while traditional dialysis filters do not remove sugammadex, high flux dialysis has been shown to remove 69% of sugammadex in a single dialysis run.

The Calgary Clinical Pharmacology physician consultation service is available Mon-Fri, 8am-5pm. The on-call physician is listed in ROCA. Clinical Pharmacology consultations are also available through the Netcare e-referral process and through Calgary Zone Specialist Link. Click HERE for more details.

The Poison and Drug Information Service (PADIS) is available 24/7 for questions related to poisonings. Please call 1-800-332-1414 (AB and NWT) or 1-866-454-1212 (SK).

References:

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