



# REVISTA BRASILEIRA DE ANESTESIOLOGIA

Official Publication of the Brazilian Society of Anesthesiology  
[www.sba.com.br/rba/index.asp](http://www.sba.com.br/rba/index.asp)



## LETTER TO THE EDITOR

### Precipitation in Gallipoli: Sugammadex / Amiodarone & Sugammadex / Dobutamine & Sugammadex / Protamine

Dear Editor,

Sugammadex is a modified gamma cyclodextrin<sup>1-3</sup>. Cyclodextrins are water soluble cyclic oligosaccharides with a lipophilic core. Sugammadex has quickly found a place in clinical use for selective antagonism of neuromuscular blockade with rocuronium<sup>1-3</sup>. Sugammadex quickly encapsulates steroidal neuromuscular blockers, increasing the amount of encapsulated steroidal neuromuscular blockers in plasma and separating the blockers from the nicotinic acetylcholine receptors<sup>1-3</sup>.

Apart from its use with steroidal neuromuscular blockers, it is known that sugammadex interacts with over 40 lipophilic, steroidal and non-steroidal drugs. These drugs include: propofol, thiopental, fentanyl, remifentanyl, vancomycin, gentamicin, salbutamol, aminophylline, atropine, digoxin, ephedrine, phentolamine, verapamil, cortisone and hydrocortisone<sup>4</sup>.

Previous research shows that, apart from steroidal muscle relaxants, sugammadex forms precipitates with protamine<sup>5</sup>.

There is no clinical data on whether sugammadex forms precipitates with other drugs, commonly used in clinical practice. The hypothesis of this study is to investigate whether the chemical and physical properties of sugammadex would contribute to a precipitation reaction with drugs commonly used in clinical practice.

With this aim, simply 0.1 mL containing 100 mg.mL<sup>-1</sup> sugammadex was mixed on a glass slide with the same volume of a drug and the presence or absence of precipitation was determined under the microscope. The drugs investigated are all commonly used in clinical anesthesia practice. They include: adrenalin (1 mg.mL<sup>-1</sup>), atropine (1 mg.mL<sup>-1</sup>), amiodarone (50 mg.mL<sup>-1</sup>), aminophylline (24 mg.mL<sup>-1</sup>), ornidazole (500 mg.3 mL<sup>-1</sup>), bupivacaine (5 mg.mL<sup>-1</sup>), cefazolin sodium (250 mg.mL<sup>-1</sup>), dexmedetomine (100 µg.mL<sup>-1</sup>), dobutamine (12.5 mg.mL<sup>-1</sup>), dopamine (8 mg.mL<sup>-1</sup>), ephedrine (0.05 g.mL<sup>-1</sup>), esmolol (10 mg.mL<sup>-1</sup>), esomeprazole (40 mg.mL<sup>-1</sup>), etomidate (2 mg.mL<sup>-1</sup>), fentanyl (50 µg.mL<sup>-1</sup>), flumazenil (0.1 mg.mL<sup>-1</sup>),

furosemide (10 mg.mL<sup>-1</sup>), gentamicin (40 mg.mL<sup>-1</sup>), glyceryl trinitrate (5 mg.mL<sup>-1</sup>), heparin (1,000 IU.mL<sup>-1</sup>), hydrocortisone (250 mg.mL<sup>-1</sup>), crystallized insulin (100 IU.mL<sup>-1</sup>), Calcium (Calcium Gluconate Monohydrate 225 mg.10 mL<sup>-1</sup> + Calcium levulinate dihydrate 572 mg.10 mL<sup>-1</sup>), ketamine (50 mg.mL<sup>-1</sup>), levobupivacaine (7.5 mg.mL<sup>-1</sup>), magnesium sulphate (1.2 mEq.mL<sup>-1</sup>), metamizol sodium (0.5 g.mL<sup>-1</sup>), methylergobasin maleate (0.2 mg.mL<sup>-1</sup>), metoclopramide (5 mg.mL<sup>-1</sup>), metoprolol (1 mg.mL<sup>-1</sup>), morphine (0.01 g.mL<sup>-1</sup>), midazolam (5 mg.mL<sup>-1</sup>), n-acetylcysteine (100 mg.mL<sup>-1</sup>), naloxone (0.4 mg.mL<sup>-1</sup>), neostigmine (0.5 mg.mL<sup>-1</sup>), nitroprusside (12 mg.mL<sup>-1</sup>), noradrenaline (1 mg.mL<sup>-1</sup>), oxytocin (5 IU.mL<sup>-1</sup>), paracetamol (10 mg.mL<sup>-1</sup>), thiopental sodium (25 mg.mL<sup>-1</sup>), pethidine (50 mg.mL<sup>-1</sup>), pheniramine (22.75 mg.mL<sup>-1</sup>), phenytoin (50 mg.mL<sup>-1</sup>), piracetam (1 g.5 mL<sup>-1</sup>), prednisolone (25 mg), prilocaine (20 mg.mL<sup>-1</sup>), propafenone (3.5 mg.mL<sup>-1</sup>), protamine hydrochloride (1,000 IU.mL<sup>-1</sup>), potassium (1 mEq.mL<sup>-1</sup>), remifentanyl (5 mg.mL<sup>-1</sup>), cefuroxime axetil (125 mg.mL<sup>-1</sup>), sulbactam-ampicillin (200 mg.mL<sup>-1</sup>), succinylcholine (20 mg.mL<sup>-1</sup>), tenoxicam (10 mg.mL<sup>-1</sup>), theophylline (24 mg.mL<sup>-1</sup>), tramadol (50 mg.mL<sup>-1</sup>), and vitamin K (10 mg.mL<sup>-1</sup>). A scale of 0-4 was used to evaluate the test, with 0 being no precipitation and 4+ being strong precipitation.

Within seconds, sugammadex (100 mg.mL<sup>-1</sup>) scored 4+ precipitation with amiodarone (50 mg.mL<sup>-1</sup>), dobutamine (12.5 mg.mL<sup>-1</sup>) and protamine hydrochloride (1,000 IU.mL<sup>-1</sup>).

There are reports on the incompatibility and precipitation of anesthetic drugs<sup>5-7</sup>. Thiopental, with basic pH, reacts with acidic muscle relaxants such as suxamethonium, mivacurium, vecuronium and rocuronium, causing precipitation<sup>8</sup>. Similarly, thiopental causes precipitation with local anesthetics due to pH differences<sup>9</sup>. Previous experimental studies have shown that thiopental reacting with various drugs may form thiopental acid crystals due to precipitation, which may cause pulmonary embolism<sup>10</sup>. Sugammadex has a pH of 7.5 and the precipitation reaction with protamine may be related to the molecules' ionic weight<sup>1-5</sup>.

Our study shows that sugammadex reacts with amiodarone, dobutamine and protamine under in-vitro conditions, causing precipitation. We emphasize that sugammadex should not be given intravenously simultaneously with these drugs. Future studies will characterize their precipitation reaction, which seems to be only the tip of the iceberg. In addition, future studies should be focused on investigating sugammadex compatibility with other drugs by using Gas Chromatography/Mass Spectrometry device. We believe the effects of this precipitation on the drugs' efficacy and circulation warrants further research.

*\*Volkan Hanci, MD, Assoc. Prof.*

*\*\*Hasan Ali Kiraz, MD, Assist. Prof.*

*\*\*Dilek Ömür, MD, Assist. Prof.*

*\*\*Serpil Ekin, MD, Assistant Doctor*

*\*\*Berna Uyan, MD, Assistant Doctor*

*\*\*\*Bulent Serhan Yurtlu, MD, Assist. Prof.*

*Departments of Anaesthesiology and Reanimation,*

*\* Dokuz Eylul University*

*(formerly Canakkale Onsekiz Mart University)*

*\*\* Canakkale Onsekiz Mart University*

*\*\*\* Dokuz Eylul University (formerly Bulent Ecevit University), Turkey*

## References

1. Naguib M - Sugammadex: another milestone in clinical neuromuscular pharmacology. *Anesth Analg*, 2007;104:575-581.
2. Brull SJ, Naguib M - Selective reversal of muscle relaxation in general anesthesia: focus on sugammadex. *Drug Des Devel Ther*, 2009;3:119-129.
3. Rex C, Bergner UA, Pühringer FK - Sugammadex: a selective relaxant-binding agent providing rapid reversal. *Curr Opin Anaesthesiol*, 2010;23:461-465.
4. Zhang M-Q - Drug-specific cyclodextrins: the future of rapid neuromuscular block reversal? *Drugs Future*. 2003;28:347-354.
5. Alston TA - Precipitation of sugammadex by protamine. *J Clin Anesth*, 2011;23:593.
6. Smith RP, Jones M - Precipitation in Manchester: ketorolac/cyclizine. *Anaesthesia*, 2001;56:494-495.
7. Ackland G - Physical incompatibility between atracurium and intravenous diclofenac. *Anaesthesia*, 2001;56:294.
8. Khan S, Stannard N, Greijn J - Precipitation of thiopental with muscle relaxants: a potential hazard. *JRSM Short Rep*, 2011;2:58.
9. Waters JH, Rizzo VL, Ramanathan S - A re-evaluation of the ability of thiopental to identify cerebrospinal fluid in epidural catheter aspirate. *J Clin Anesth*, 1995;7:224-227.
10. Taniguchi T, Yamamoto K, Kobayashi T - Precipitate formed by thiopentone and vecuronium causes pulmonary embolism. *Can J Anaesth*, 1998;45:347-351.



# REVISTA BRASILEIRA DE ANESTESIOLOGIA

Official Publication of the Brazilian Society of Anesthesiology  
www.sba.com.br/rba/index.asp



## CARTA AO EDITOR

### Precipitação em Gallipoli: Sugamadex/Amiodarona & Sugamadex/Dobutamina & Sugamadex/Protamina

Caro Editor,

Sugamadex é uma gama-ciclodextrina modificada<sup>1-3</sup>. As ciclodextrinas são oligossacarídeos cíclicos solúveis em água com um núcleo lipofílico. Sugamadex encontrou rapidamente um lugar no uso clínico como um reversor seletivo do bloqueio neuromuscular<sup>1-3</sup>. Sugamadex encapsula rapidamente os agentes bloqueadores neuromusculares esteroides, aumenta a quantidade desses agentes no plasma e separa esses bloqueadores dos receptores nicotínicos de acetilcolina<sup>1-3</sup>.

Além de seu uso com agentes bloqueadores neuromusculares esteroides, sabe-se que sugamadex interage com mais de 40 fármacos lipofílicos, esteroides e não esteroides, que incluem propofol, tiopental, fentanil, remifentanil, vancomicina, gentamicina, salbutamol, aminofilina, atropina, digoxina, efedrina, fentolamina, verapamil, cortisona e hidrocortisona<sup>4</sup>.

Pesquisa anterior mostra que, além dos relaxantes musculares esteroides, sugamadex forma precipitados com protamina<sup>5</sup>.

Não há dados clínicos sobre a formação de precipitados de sugamadex com outros medicamentos habitualmente usados na prática clínica. A hipótese deste estudo é investigar se as propriedades químicas e físicas de sugamadex contribuiriam para uma reação de precipitação com medicamentos comumente usados na prática clínica.

Com esse objetivo, apenas 0,1 mL contendo sugamadex 100 mg.mL<sup>-1</sup> foi misturado sobre uma lâmina de vidro com o mesmo volume de um fármaco e a presença ou ausência de precipitação foi determinada sob o microscópio. Os fármacos investigados são de uso comum na prática da anestesiologia e incluem: adrenalina (1 mg.mL<sup>-1</sup>), atropina (1 mg.mL<sup>-1</sup>), amiodarona (50 mg.mL<sup>-1</sup>), aminofilina (24 mg.mL<sup>-1</sup>), ornidazol (500 mg.3 mL<sup>-1</sup>), bupivacaína (5 mg.mL<sup>-1</sup>), cefazolina sódica (250 mg.mL<sup>-1</sup>), dexmedetomina (100 µg.mL<sup>-1</sup>), dobutamina (12,5 mg.mL<sup>-1</sup>), dopamina (8 mg.mL<sup>-1</sup>), efedrina (0,05 g.mL<sup>-1</sup>), esmolol (10 mg.mL<sup>-1</sup>), esomeprazol (40 mg.mL<sup>-1</sup>), etomidato (2 mg.mL<sup>-1</sup>), fentanil (50 µg.mL<sup>-1</sup>), flumazenil (0,1 mg.mL<sup>-1</sup>),

furosemda (10 mg.mL<sup>-1</sup>), gentamicina (40 mg.mL<sup>-1</sup>), gliceril trinitrato (5 mg.mL<sup>-1</sup>), heparina (1.000 IU.mL<sup>-1</sup>), hidrocortisona (250 mg.mL<sup>-1</sup>), insulina cristalizada (100 IU.mL<sup>-1</sup>), cálcio (gluconato de cálcio monohidratado 225 mg.10 mL<sup>-1</sup> + levulinato de cálcio dihidratado 572 mg.10 mL<sup>-1</sup>), cetamina (50 mg.mL<sup>-1</sup>), levobupivacaína (7,5 mg.mL<sup>-1</sup>), sulfato de magnésio (1,2 mEq.mL<sup>-1</sup>), metamizol sódico (0,5 g.mL<sup>-1</sup>), maleato de metil ergobasina (0,2 mg.mL<sup>-1</sup>), metoclopramida (5 mg.mL<sup>-1</sup>), metoprolol (1 mg.mL<sup>-1</sup>), morfina (0,01 g.mL<sup>-1</sup>), midazolam (5 mg.mL<sup>-1</sup>), n-acetilcisteína (100 mg.mL<sup>-1</sup>), naloxona (0,4 mg.mL<sup>-1</sup>), neostigmina (0,5 mg.mL<sup>-1</sup>), nitroprussiato (12 mg.mL<sup>-1</sup>), noradrenalina (1 mg.mL<sup>-1</sup>), ocitocina (5 IU.mL<sup>-1</sup>), paracetamol (10 mg.mL<sup>-1</sup>), tiopental sódico (25 mg.mL<sup>-1</sup>), petidina (50 mg.mL<sup>-1</sup>), feniramina (22,75 mg.mL<sup>-1</sup>), fenitoína (50 mg.mL<sup>-1</sup>), piracetam (1 g.5 mL<sup>-1</sup>), prednisolona (25 mg), prilocaína (20 mg.mL<sup>-1</sup>), propafenona (3,5 mg.mL<sup>-1</sup>), cloridrato de protamina (1.000 IU.mL<sup>-1</sup>), potássio (1 mEq.mL<sup>-1</sup>), remifentanil (5 mg.mL<sup>-1</sup>), axetil cefuroxima (125 mg.mL<sup>-1</sup>), ampicilina/sulbactam (200 mg.mL<sup>-1</sup>), succinilcolina (20 mg.mL<sup>-1</sup>), tenoxicam (10 mg.mL<sup>-1</sup>), teofilina (24 mg.mL<sup>-1</sup>), tramadol (50 mg.mL<sup>-1</sup>) e vitamina K (10 mg.mL<sup>-1</sup>). Uma escala de 0-4 foi usada para avaliar o teste, sendo 0 = sem precipitação e 4+ = forte precipitação.

Em poucos segundos, sugamadex (100 mg.mL<sup>-1</sup>) atingiu o escore de 4+ para precipitação com amiodarona (50 mg.mL<sup>-1</sup>), dobutamina (12,5 mg.mL<sup>-1</sup>) e cloridrato de protamina (1.000 IU.mL<sup>-1</sup>).

Há relatos sobre a incompatibilidade e precipitação de drogas anestésicas<sup>5-7</sup>. Tiopental, com pH básico, reage com relaxantes musculares ácidos, como suxametônio, mivacúrio, vecurônio e rocurônio e causa a precipitação<sup>8</sup>. Do mesmo modo, tiopental causa precipitação com anestésicos locais por causa de diferenças no pH<sup>9</sup>. Estudos experimentais anteriores mostraram que tiopental em reação com vários fármacos pode formar cristais de ácido por causa da precipitação, o que pode causar embolia pulmonar<sup>10</sup>. Sugamadex tem um pH de 7,5 e a reação de precipitação com protamina pode estar relacionada ao peso das moléculas iônicas<sup>1-5</sup>.

O nosso estudo mostra que sugamadex reage com amiodarona, dobutamina e protamina sob condições in vitro e causa precipitação. Salientamos que sugamadex não deve ser administrado por via intravenosa em concomitância com esses fármacos. Estudos futuros irão caracterizar sua reação de precipitação, o que parece ser apenas a ponta do iceberg. Além disso, os estudos futuros devem estar focados em investigar a compatibilidade de sugamadex com outros fármacos com o uso do dispositivo de cromatografia gasosa com espectrometria de massa. Nós acreditamos que os efeitos dessa precipitação na eficácia e circulação dos fármacos justificam pesquisas adicionais.

*\*Volkan Hanci, Médico, Professor*

*\*\*Hasan Ali Kiraz, Médico, Professor*

*\*\*Dilek Ömür, Médico, Professor*

*\*\*Serpil Ekin, Médico Assistente*

*\*\*Berna Uyan, Médico Assistente*

*\*\*\*Bulent Serhan Yurtlu, Médico, Professor*

*Departamento de Anestesiologia e Reanimação,*

*\* Dokuz Eylul University*

*(formerly Canakkale Onsekiz Mart University)*

*\*\* Canakkale Onsekiz Mart University*

*\*\*\* Dokuz Eylul University (formerly Bulent Ecevit University), Turquia*

## Referências

1. Naguib M - Sugammadex: another milestone in clinical neuromuscular pharmacology. *Anesth Analg*, 2007;104:575-581.
2. Brull SJ, Naguib M - Selective reversal of muscle relaxation in general anesthesia: focus on sugammadex. *Drug Des Devel Ther*, 2009;3:119-129.
3. Rex C, Bergner UA, Pühringer FK - Sugammadex: a selective relaxant-binding agent providing rapid reversal. *Curr Opin Anaesthesiol*, 2010;23:461-465.
4. Zhang M-Q - Drug-specific cyclodextrins: the future of rapid neuromuscular block reversal? *Drugs Future*. 2003;28:347-354.
5. Alston TA - Precipitation of sugammadex by protamine. *J Clin Anesth*, 2011;23:593.
6. Smith RP, Jones M - Precipitation in Manchester: ketorolac/cyclizine. *Anaesthesia*, 2001;56:494-495.
7. Ackland G - Physical incompatibility between atracurium and intravenous diclofenac. *Anaesthesia*, 2001;56:294.
8. Khan S, Stannard N, Greijn J - Precipitation of thiopental with muscle relaxants: a potential hazard. *JRSM Short Rep*, 2011;2:58.
9. Waters JH, Rizzo VL, Ramanathan S - A re-evaluation of the ability of thiopental to identify cerebrospinal fluid in epidural catheter aspirate. *J Clin Anesth*, 1995;7:224-227.
10. Taniguchi T, Yamamoto K, Kobayashi T - Precipitate formed by thiopentone and vecuronium causes pulmonary embolism. *Can J Anaesth*, 1998;45:347-351.