

New way of dosing sugammadex for termination of vecuronium induced neuromuscular block

Nov način odmerjanja sugamadeksa za odpravo z vekuronijem povzročene živčno-mišične blokade

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Ključne besede:

sugamadex; vekuronij;
rocuronij; živčnomišična
blokada

Key words:

sugammadex;
vecuronium;
neuromuscular block;
rocuronium

Citirajte kot/Cite as:

Zdrav Vestn 2015;
84: 439–46

Prispelo: 24. feb. 2014,
Sprejeto: 7. maj 2015

Izvleček

Uvod in namen: Sugamadex je novo zdravilo, ki selektivno veže živčno-mišične relaksante aminosteroidne skupine (vekuronij, rocuronij). Z vezavo prepreči njihovo delovanje in tako prekine živčno-mišično relaksacijo. Vsaka molekula sugamadeksa veže eno molekulo živčno-mišičnega relaksanta. Za vzpostavitev živčno-mišične blokade je potrebnih manj molekul vekuronija kot rocuronija. Teoretično bi za prekinitve z vekuronijem povzročene živčno-mišične blokade potrebovali manj molekul sugamadeksa kot pri prekinitvi z rocuronijem povzročene živčno-mišične blokade. Nov način odmerjanja sugamadeksa prilagodi odmerek sugamadeksa glede na količino vekuronija, uporabljenega med operacijo in globino živčno-mišične blokade ob koncu operacije. Namen naše študije je primerjati uspešnost novega načina odmerjanja sugamadeksa z uspešnostjo neostigmina v kombinaciji z atropinom pri odpravi živčno-mišičnega bloka, povzročene z vekuronijem.

Metode: V študijo smo vključili 20 odraslih bolnikov, ki so potrebovali splošno anestezijo za svojo operacijo in so med njo prejeli sugamadex ali neostigmin. Skupina 11 bolnikov (SUG) je ob koncu operacije prejela odmerek sugamadeksa za prekinitve živčno-mišičnega bloka, ki je bil prilagojen glede na teoretični izračun. Druga skupina 9 bolnikov (NEO) je ob koncu operacije za prekinitve živčno-mišičnega bloka prejela neostigmin/atropin. Živčno-mišično blokado smo med operacijo spremljali z akcelarometrično metodo merjenja globine živčno-mišične relaksacije (TOF watch- Organon, Nizozemska). Med skupinama smo nato primerjali čas po odmerku sredstva za odpravo živčno-mišičnega bloka, ki je bil potreben, da je vrednost razmerja moči prve in zadnje kontrakcije m. adductor pollicis v seriji štirih znašala 0,9. Z ekonomskega stališča smo primerjali odmerke sugamadeksa, dane

bolnikom med študijo, s standardnimi odmerki, ki bi jih sicer ti bolniki prejeli, če bi odmerjali sugamadex na kilogram telesne mase.

Rezultati: Povprečen čas, potreben za odpravo živčno-mišične blokade v skupini SUG, je bil 5,12 min, v skupini NEO pa 12,6 min ($P < 0,05$). V skupini SUG nismo opazili ali izmerili primerne pooperativne rekurarizacije. Za vse bolnike v skupini SUG smo porabili skupno 530 mg sugamadeksa. Če bi odmerjali po standardni shemi, bi porabili 2420 mg sugamadeksa.

Zaključek: Nov način odmerjanja sugamadeksa učinkovito in zanesljivo odpravi živčno-mišično blokado, vzpostavljeno z vekuronijem, ne glede na vrednost TOF ob koncu operacije. Ekonomsko gledano se strošek sugamadeksa zmanjša za 80 EUR na povprečnih 20 EUR na bolnika.

Abstract

Background and Goal of Study: Sugammadex is a selective binding agent that binds aminosteroid muscle relaxants. Each molecule of sugammadex binds one molecule of muscle relaxant. To produce the same depth of the neuromuscular block (NMB) much less molecules of vecuronium are needed than molecules of rocuronium. In theory less sugammadex would be needed to neutralize the neuromuscular block if vecuronium was used to produce the neuromuscular block. Our aim was to compare reversal of vecuronium induced muscle relaxation between a new way of dosing sugammadex, which takes into account TOF value at the end of the surgery and the amount of vecuronium given during the surgery with neostigmine atropine combination. We also wanted to know how much this dosage regime can save compared to standard per kg dosage.

Materials and Methods: 20 adult patients requiring a general anesthesia for surgery were analyzed. The first group of 11 patients (SUG)

received sugammadex at the end of the surgery according to the table one for NMB reversal. The second group of 9 patients (NEO) received neostigmine and atropine. Train of four (TOF) value was recorded at the end of the surgery and then continuously until the TOF value reached more than 0.9 and the patient was extubated. The time required for the TOF value reaching 0.9 was compared between the groups. For economical evaluation we compared the amount of sugammadex used in the SUG group to standard sugammadex per kg dosage.

Results and Discussion: Mean time to recovery to a TOF ratio of 0.9 with sugammadex was 5.12

min versus 12.6 min with neostigmine atropine ($P < 0.05$). No sign of postoperative residual curarisation was observed in the SUG group. For patients in our study 530 mg of sugammadex were used to neutralize the NMB. If standard per kg sugammadex dosing had been used we would have used 2420 mg for the NMB reversal.

Conclusion(s): New dosing for sugammadex was successful in neutralizing the NMB regardless of the TOF value at the end of the surgery. The economic impact of the proposed dosing is significant as an average cost for the vecuronium NMB reversal is reduced from around 80 € to 20 € per patient.

Background and Goal of Study

Sugammadex is a new drug for termination of the neuromuscular block produced by steroidal muscle relaxants (rocuronium and vecuronium). Structurally it is gamma-cyclodextrine with molar mass of 2178. One molecule of sugammadex binds one molecule of the muscle relaxant in its lipophilic core and makes the molecule of the muscle relaxant inactive. Rocuronium displays the highest affinity for sugammadex followed by vecuronium and pancuronium which displays the lowest affinity.¹⁻² Compared to older drugs it lacks the muscarinic side effect because it binds steroidal muscle relaxant molecules instead of terminating the neuromuscular block via acetylcholine esterase inhibition pathway.³ So far it has been shown that it is safe even in larger dosages and has almost no side effects. The most important distinction between acetylcholine esterase inhibitors and sugammadex is that sugammadex can reliably and predictably completely terminate the neuromuscular block at any depth which acetylcholine esterase inhibitors cannot.⁴⁻⁸ Sugammadex binds rocuronium or vecuronium in 1:1 fashion. The current dosage for sugammadex administration is set per kg and TOF monitor stimulation result at the time of reversal. For a deep neuromuscular block at presence 1–2 twitches after posttetanic stimulation 4 mg/kg is recommended dose. When the neuromuscular block has par-

tially recovered and two twitches or more can be seen on TOF monitor 2 mg/kg is the recommended dosage. Both dosages reliably terminate rocuronium or vecuronium induced neuromuscular blockade. 16 mg/kg is recommended if immediate reversal of the neuromuscular block after 1.2 mg/kg of rocuronium is needed.⁹ Studies have also been published that tested much smaller dosages for termination of rocuronium induced neuromuscular blockade at appearance of the fourth twitch on TOF monitor and at level of 50 % TOF value. Both studies confirmed that smaller dosages than 2mg/kg are effective in terminating the neuromuscular block. 1 mg/kg or 0.5 mg/kg in case of reappearance of the fourth twitch on TOF monitor and 0.25 mg/kg in case of TOF ratio 50 % or more.^{10,11} For vecuronium similar studies haven't been made so far.¹²

As was already described in case report termination of the vecuronium induced neuromuscular block with much smaller dosages of sugammadex is possible than dosing per kg would suggest.¹³ In the case report different formulation for estimating adequate dosage of sugammadex was used. To successfully terminate the vecuronium induced neuromuscular block sugammadex dose was adjusted to amount vecuronium given during the surgery rather than patient's weight. Because fewer molecules of vecuronium are needed per kilogram to

produce the same level of the neuromuscular block compared to rocuronium (1×10^{17} compared to 6.8×10^{17}) it was concluded that fewer molecules of sugammadex could successfully neutralize vecuronium induced neuromuscular block. In this study we wanted to compare this principle to the standard neostigmine neuromuscular block reversal

Methods

Study protocol was approved by the Slovenian national ethics committee. Study was designed as prospective observational study. After written informed consent 20 adult patients ASA 1–3 requiring a general anesthesia and endotracheal intubation were included in the study. After an intravenous cannula was placed in the right or left forearm anesthesia was induced with propofol 2–3 mg/kg and fentanyl 2–4 mcg/kg injected into fast running intravenous infusion at the preference of each anesthesiologist. After the loss of consciousness TOF monitor (TOF-Watch monitor, Organon, Oss, The Netherlands) was calibrated and the patients received 0.1 mg/kg of vecuronium. The patients were intubated 3 min after vecuronium administration. Anesthesia was maintained with sevoflurane or isoflurane. During surgery TOF value was continuously measured and vecuronium was additionally given to the patients as needed to maintain adequate neuromuscular blockade. TOF value was recorded at the end of the surgery and reversal drug was given each patient. Patient either received sugammadex (SUG group) or neostigmine (NEO group) at the preference of each anesthesiologist. Sugammadex was administered according to table one as is usual practice in our hospital. Table one represent vecuronium adjusted sugammadex dose for each level of neuromuscular blockade. Dose adjustment was already described before.¹³ Short description in provided below.

First we calculated how many molecules of sugammadex are administered to a patient per kilogram of body weight in case of deep (4 mg/kg) or shallow (2 mg/kg) neuromuscular block. Number of sugammadex molecules was divided by the number of rocuronium molecules in a single bolus dose of

0.6 mg/kg. The result is called sugammadex/rocuronium ratio (SR ratio). SR ratio represents how many molecules of sugammadex are administered to a patient after he or she received a single bolus dose of 0.6 mg/kg of rocuronium. In case of deep neuromuscular block 1.6 molecule of sugammadex is administered for each molecule of rocuronium. In case of shallow neuromuscular block 0.8 molecule of sugammadex is administered for each molecule of rocuronium. Residual neuromuscular block was defined as TOF value of 3 or more. SR ratio 0.5 was arbitrary set for the purpose of calculating sugammadex dose. Meaning 0.5 molecule of sugammadex is administered for each molecule of rocuronium.

To calculate the number of sugammadex molecules needed to neutralize vecuronium induced neuromuscular block we multiplied number of vecuronium molecules patient received during entire surgery by SR ratio. In this way ratio of sugammadex molecules and vecuronium molecules for each level of neuromuscular block was the same as in case of rocuronium induced neuromuscular blockade. We used the whole amount of vecuronium during surgery because vecuronium has active metabolites which also bind to sugammadex.

Number of sugammadex molecules was further multiplied by 1.5 because vecuronium has lower affinity for sugammadex.⁴ Factor 1.5 was arbitrary set and was also implemented because of other possible unknown factors that could play a role in termination of vecuronium induced neuromuscular block by sugammadex.

For easier clinical use appropriate dose of sugammadex was calculated for all three levels of neuromuscular blockade for a total dose of 6, 8, 10, 12 and 14 mg of vecuronium during surgery. Results were empirically rounded up or down and are represented in table one.

To select relevant sugammadex dose from table one the total amount of vecuronium (mg) must be cross matched to appropriate level of neuromuscular block that is present at the end of surgery.

Additional 10–20 mg bolus of sugammadex was given if after 8 min TOF value didn't

reach 0.9 after first bolus dose selected from table one.

Neostigme was given 0.035 mg/kg with concurrent dose of atropine 0.01 mg/kg as is usually administered in our hospital. TOF value was continuously recorded until it reached more than 0.9 and the patient was extubated. The time required for the TOF value to reach 0.9 was primary end point and was compared between the groups. We also arbitrarily set clinical relevant time to 15 min for reversal of NMB after injection of reversal agent. Reversal was considered clinically unsuccessful if it was longer than 15 min. TOF value was also measured in recovery area to monitor if TOF value in any patient in the SUG group fell back below 0.9. Results were statistically analyzed using one way ANOVA. For economical evaluation we compared the amount of sugammadex used in the SUG group to standard sugammadex dose.

Results

11 patients received sugammadex at the end of the surgery – sugammadex group (SUG) and 9 patients received neostigmine –neostigmine group (NEO). In SUG group 6 patients had abdominal surgery, 3 patients had orthopedic surgery, 1 patient had ENT surgery and 1 patient had gynecological surgery. In NEO group 8 patients had abdominal surgery and 1 patient had gynecological surgery. Demographic data and level of neuromuscular blockade at the end

of surgery before administration of reversal drug were similar between two groups and are represented in table two and three. Average time to 0.9 TOF in SUG group was 306.5 s (72 s–648 s) compared to average 756.8 s (92 s–1500 s) in NEO group p value being less than 0.05. We haven't observed any recuraristion effect in the SUG group. All patients in the SUG group recovered to TOF > 0.9 in clinically relevant time. Three out of nine patients in the NEO group failed to reach TOF ratio value 0.9 or more in clinically relevant time. 4 out of 11 of patients received additional 10–20 mg bolus dose of sugammadex. When we compared economic impact it was clearly seen that far less sugammadex was used with proposed dosing than when standard dosing is used. For 11 patients we used 530 mg of sugammadex. If standard dosing was used, 2420 mg of sugammadex would have been spent for the neuromuscular block reversal. Representation of the table one dosage and standard per kg dosage of sugammadex for each patient is shown on graph one.

Discussion

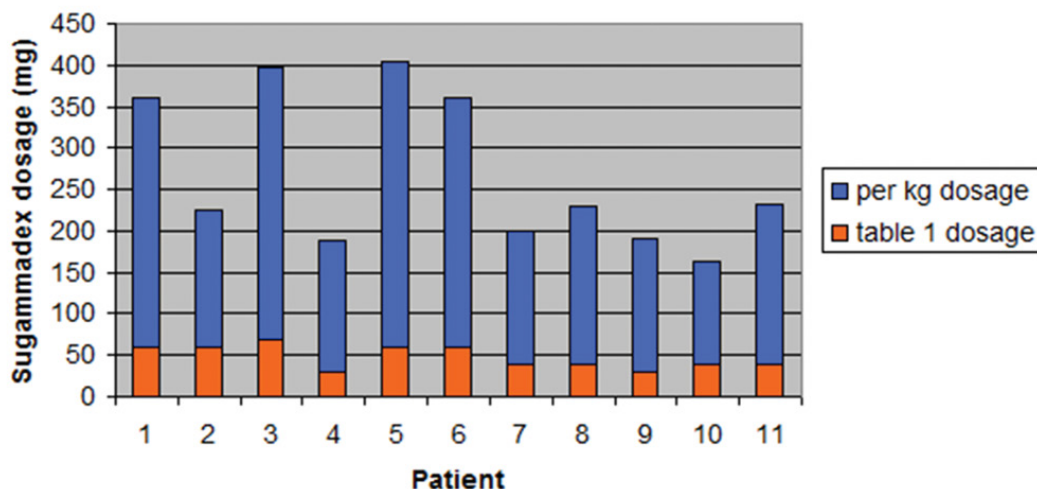
Results show that the proposed dosage regime is more successful in terminating any depth of the neuromuscular block compared to neostigmine. Baseline clinical characteristics of the two groups were similar and should not have caused any relevant effect on TOF value recovery. Our results are in line with other studies that have al-

Table 1: Sugammadex dose (mg).

Vecuronium (mg)	TOF value		
	0	1 or 2	3 or more
6	40	35	30
8	60	40	40
10	60	50	40
12	75	60	40
14	90	70	50

To select the appropriate sugammadex dose one must cross-match relevant vecuronium dose and TOF value at the time of reversal.

Figure 1: Representation amount of sugammadex given according to Table 1 and standard amount of sugammadex in case of each individual patient.



ready compared neostigmine reversal times to sugammadex reversal times.⁶⁻⁸ Although our sugammadex reversal times are longer than ones already published where 2 or 4 mg per kg of sugammadex is used it is still fast enough that it did not hinder busy clinical setting in our hospital.⁶⁻⁸ Similar phenomenon was observed by Pongrácz A. et al. when they used 0.5 mg/kg sugammadex for reversal rocuronium NMB at reappearance of T₄. The idea of smaller dosages for shallow blocks is not new and was described before by Schaller et al. At higher TOF ratios some of rocuronium's molecules from initial dose are already metabolized and it is logical that fewer molecules of sugammadex are needed to neutralize them because of 1:1 binding ratio. The same principle might apply for NMB that is produced by vecuronium.

As we described in our case report fewer molecules of vecuronium are needed to produce the same depth of the neuromuscular block compared to rocuronium. Roughly 1×10^{17} molecules of vecuronium compared to 6.8×10^{17} for rocuronium.¹³ It is rational to conclude that fewer molecules need to be encapsulated by sugammadex to neutralize the neuromuscular block and thus less sugammadex can be administered to terminate the neuromuscular block.

4 out of 11 patients, who received sugammadex, needed additional bolus 10–20 mg of sugammadex to reach TOF value 0.9 in clinical relevant time. This shows that our calculations are not suitable for all patient populations. There are obviously other unknown factors that have to be taken into consideration when determining the exact

Table 2: Demographic data.

	Neostigmine Group	Sugammadex Group
n	9	11
Mean age (SD), yr	52 (10.2)	52.2 (16.3)
Male:female, n	5:4	5:6
Mean weight (SD), kg	82.6 (11.7)	81.2 (9.0)
ASA physical status I:II:III	4:5:0	7:3:1

ASA = American Society of Anesthesiologists

amount of sugammadex needed to reverse vecuronium induced neuromuscular block in under 15 min time and further studies are needed to identify them.

Recurarization or rebound effect has not been observed in any patient in the SUG group. Sugammadex rebound is a phenomenon where TOF ratio decline is observed after initial recovery of TOF ratio to 0.9. It has been previously described in some case reports where patients received inadequate sugammadex dose for rocuronium neuromuscular block neutralization.^{5,14-15} We haven't observed such phenomenon in any of our patients in the SUG group despite very low dose per kg if compared to standard dosing. Why this is the case we can only speculate and so called rebound phenomenon should be addressed in future sugammadex studies.

When standard dosing per kg is used for vecuronium induced neuromuscular block neutralization a large portion of sugammadex molecules remain unbound as fewer molecules need to be encapsulated.¹³ With standard dosing the patient receives 5.5×10^{17} number of molecules per kg of sugammadex for neutralization of 1×10^{17} number of molecules per kg of vecuronium when TOF value is 2 or more. In this setting more than 4×10^{17} molecules of sugammadex remain free of vecuronium. These free molecules represent obstacle for rocuronium or vecuronium to induce neuromuscular block after sugammadex administration in case of reoperation as was already described by Sakai et al. in their case report.¹⁶ Because of lower dose that is used with the table one dosing fewer free molecules of sugammadex are left and inducing the neuromuscular block could be easier. The manufacturer

recommends a 4 h delay before rocuronium or vecuronium is used again after sugammadex administration.⁹ With dose adjustment according to the table one induction of the neuromuscular block with rocuronium or vecuronium after use of sugammadex could be successful sooner than after a period of 4 h but that has yet to be proven.

Until now reported incidence of sugammadex related side effects is very low.¹² The most predominant serious side effect is allergy or allergy like reaction. Its incidence is low as only few cases have been described so far.¹⁷⁻¹⁸ Laboratory studies on rats and cell cultures have shown some possible side effects.¹⁹⁻²¹ Kalkan et al. showed that rocuronium and sugammadex remain in the circulation for a long time and they may cause skeletal and cardiac muscle myopathy and weakening of the muscle fibers.¹⁹ Rats receiving rocuronium and high doses of sugammadex (96 mg/kg) showed histological changes on kidneys such as glomerular vacuolation, tubular dilatation, vascular vacuolation, hypertrophy and lymphocyte infiltration.²⁰ A study on neuron cell cultures by Palanca et al. showed sugammadex induced neuron apoptosis which was induced by free sugammadex molecules via cholesterol regulation pathway.²¹ These experimental side effect could be dose-dependent. With this in mind we presume that lower sugammadex doses are less likely to cause any of those side effects in real clinical setting. Economic impact is very promising because of lowering the cost of sugammadex for each patient. For 11 patients in our study 75 % less sugammadex was used compared to standard dosing. Thus the proposed dosing regime could make sugammadex viable in eve-

Table 3: Level of neuromuscular blockade before reversal drug administration.

	Neostigmine Group	Sugammadex Group
TOF value 0, n (%)	2 (22.2)	3 (27.2)
TOF value 1 or 2, n (%)	2(22.2)	4 (36.4)
TOF value 3 or more, n (%)	5(55.5)	4 (36.4)

TOF= train-of-four

ryday elective surgery because of reduction in costs that this regime offers. It would be sensible for the manufacturer to make 50 mg vials of sugammadex instead of 200 mg, so proposed dosing could be more easily adopted in everyday clinical setting. As we have already mentioned, even rocuronium could be neutralized with smaller dosages of sugammadex in certain clinical settings and smaller vials of sugammadex would be more convenient.¹⁰⁻¹¹

Conclusion

This study confirms that our theoretical calculation described in our case report can

be utilized in sugammadex dosing for everyday elective surgery if vecuronium is used. Showing that the table one was successfully adjusting sugammadex dose for each patient in everyday clinical work we see no reason in automatically administration of 2 mg/kg or 4 mg/kg of sugammadex in elective surgery when vecuronium is used. Further research is needed to additionally asses the table one in different clinical situations and to further describe formula which adjusts sugammadex dosage for neutralization of the vecuronium induced neuromuscular block at different TOF values and patient subpopulation.

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