Sugammadex after the Reappearance of Four Twitches during Train-of-four Stimulation: Monitoring and Dose Considerations

To the Editor:

I read with great interest the article by Pongrácz *et al.*[1] evaluating the appropriate dose of sugammadex to reverse neuromuscular blockade (NMB) after the reappearance of four twitches during train-of-four (TOF) stimulation. It is a welcome addition to previous studies that have demonstrated the superiority of sugammadex over anticholinesterases in completely, safely, and quickly reversing rocuronium-induced NMB of any magnitude.[1,2] This study raises two important issues, which deserve comment.

To my knowledge, this is the first clinical trial that has considered a TOF ratio of 1.0, instead of 0.9 or greater, as the goal for reversal of NMB.[1] A TOF ratio of 0.9 or greater may not indicate full recovery, as this ratio can be associated with impaired neuromuscular transmission,[3] inhibition of the hypoxic–ventilatory response, and upper airway or pharyngeal dysfunction.[4] Acceleromyography studies have confirmed the potential for inadequate reversal at a TOF ratio of 0.9 or greater, leading to the recommendation that a TOF ratio of 1.0 or greater be used to confirm complete recovery from NMB.[2,4] With the introduction of sugammadex into clinical practice, obtaining a TOF ratio of 1.0 or greater is now a relatively easy goal to achieve, and it is hoped that future research and clinical practice will follow the example shown by Pongrácz *et al.*[1] by insisting on the use of this ratio as the goal for NMB reversal.

Although Pongrácz *et al.*[1] found that 1.0 mg/kg was sufficient to achieve a TOF of 1.0 after the reappearance of four twitches on TOF stimulation, I have some concern to recommend it as the optimal dose of sugammadex in this situation. A dose of sugammadex is just sufficient to liberate approximately 30% of the postjunctional nicotinic receptors, a condition necessary for the complete reversal.[5] So, even with complete reversal of NMB by sugammadex, up to 70% of the postjunctional nicotinic receptors may remain occupied by steroidal neuromuscular-blocking agent.[5] Therefore, a larger dose of sugammadex, such as 2 mg/kg, may be more appropriate, as it will create a greater rocuronium tissue to plasma concentration gradient, thereby causing more free rocuronium molecules to move into the circulation, where they are promptly encapsulated.[5] Reducing the number of postjunctional nicotinic receptors occupied by rocuronium may reduce the risk of recurarization[6] and the neuromuscular-blocking effects of agents that decrease acetylcholine release,[5] thus further improving patient safety.[4–6]

 Anesthesiology 2014; 120:508-16

With its unique mechanism of action, proven efficacy in reversing NMB, fast onset of action, and minimal adverse effects, sugammadex has become an important tool in modern-day anesthesia practice.[2,4,5] By using a TOF ratio of 1.0 or greater as the goal for NMB reversal and administering the most appropriate dose for the degree of blockade, full potential of sugammadex for improving patient care and safety may be achieved.

Competing Interests

The author has received payment for lecture from Merck Sharp & Dohme (Italy).

Michele Carron, M.D., University of Padova, Padova, Italy. michele.carron@unipd.it

References

1. Pongrácz A, Szatmári S, Nemes R, Fülesdi B, Tassonyi E: Reversal of neuromuscular blockade with sugammadex at the reappearance of four twitches to train-of-four stimulation. Anesthesiology 2013; 119:36–42
2. Kopman AF, Brull SJ: Low-dose sugammadex reversal: There is no such thing as a free lunch. Anesthesiology 2013; 119:10–2
3. Eikermann M, Gerwig M, Hasselmann C, Fiedler G, Peters J: Impaired neuromuscular transmission after recovery of the train-of-four ratio. Acta Anaesthesiol Scand 2007; 51:226–34
4. Plaud B, Debaene B, Donati F, Marty J: Residual paralysis after emergence from anesthesia. Anesthesiology 2010; 112:1013–22
5. Bom A, Hope F, Rutherford S, Thomson K: Preclinical pharmacology of sugammadex. J Crit Care 2009; 24:29–35
6. Le Corre F, Nejmeddine S, Fatahine C, Tayar C, Marty J, Plaud B: Recurarization after sugammadex reversal in an obese patient. Can J Anaesth 2011; 58:944–7

(Accepted for publication October 17, 2013.)

In Reply:

In his letter to the Editor, Dr. Carron raises two important issues referring to the published data by Pongrácz *et al.*[1] evaluating low doses of sugammadex to reverse rocuronium-induced neuromuscular blockade (NMB) after the reappearance of four twitches during train-of-four (TOF) stimulation.

First, Dr. Carron emphasizes the importance of having considered a TOF fade ratio of 1.0 or greater as an adequate reversal in our study, unlike 0.9 or greater used by other investigators. Indeed, to date in all published studies investigating sugammadex, the primary outcome parameter was a nonnormalized TOF ratio of 0.9. However, a recorded TOF fade ratio of 0.9 does not equal full recovery of the NMB, because after sugammadex the TOF ratios regularly reach a final value of 1.0 or greater. Therefore, we considered a

nonnormalized TOF ratio of 1.0 or greater as an acceptable criterion to exclude a residual NMB.[2] Also, we calculated the normalized TOF ratios at recovery, which were around 1.0, as well. Normalization (dividing TOF fade ratios at recovery with those before administration of rocuronium) was necessary because control TOF ratios with acceleromyography often exceeded unity, biasing the results of recovery.[3] For instance, when the TOF ratio recovers to 1.0, but the control TOF ratio is 1.18, the normalized TOF ratio will be 0.84 (1.0/1.18), which is insufficient. There is general agreement that a normalized TOF ratio of 0.9 or greater is required to exclude clinically significant residual paralysis.[2,3] Furthermore, the changes of single-twitch height should also be measured during neuromuscular monitoring and should exceed a value of 90% of control for neuromuscular recovery to be considered as acceptable.[4] However, to date the majority of investigations have not described the changes of T1 single twitches. Considering all these factors, we do agree with Dr. Carron's suggestion that there is place for improvement of the current practice of neuromuscular monitoring and research.

Second, Dr. Carron estimates that 1.0 mg/kg of sugammadex is not as safe as 2.0 mg/kg in reversing a threshold TOF count 4 residual NMB and therefore suggests the administration of 2.0 mg/kg in this situation. There is no evidence for this suggestion. We have demonstrated that 1.0 mg/kg like 2.0 mg/kg of sugammadex effectively reverses rocuronium-induced NMB when administered at the reappearance of four twitches during TOF stimulation.[1] Recurrent muscle paralysis did not occur in our patients. Dr. Carron argues that the safety margin of neuromuscular transmission (70 to 75% of postsynaptic acetylcholine receptors) cannot be liberated from the rocuronium molecules when lower than 2.0 mg/kg sugammadex is administered. This assumption, although attractive, is not supported by any evidence. It is logical that at a TOF count 4 level of block fewer rocuronium molecules are present at the neuromuscular synapse than at a TOF count 2 level of block, where 2.0 mg/kg of sugammadex is the recommended dose. Because the encapsulation of rocuronium by sugammadex is a one-to-one molecular interaction,[5] one may hypothesize that the shallower the depth of block the fewer sugammadex molecules are necessary to encapsulate all of the free rocuronium molecules and to relieve the pre- and postsynaptic acetylcholine receptors. Our results support this assumption. However, a caveat is in order: unless the amount of sugammadex is sufficient for the encapsulation of almost all rocuronium molecules, agents that decrease acetylcholine release at the motor nerve terminal (*i.e.*, magnesium or aminoglycoside antibiotics) may cause recurarization. It may therefore be prudent not to give inadequately low doses of sugammadex (0.25 or 0.5 mg/kg) in patients who had received these agents. Quantifying the proportion of receptor occupancy after recommended and lower doses of sugammadex requires further research.

We estimate that adequate use of low doses of sugammadex is safe and may contribute to its widespread use by reducing the expenses of the treatment.

Competing Interests

The authors declare no competing interests.

Andrienn Pongrácz, M.D., Réka Nemes, M.D., Béla Fülesdi, M.D., Ph.D., D.Sc., Edömér Tassonyi, M.D., Ph.D., D.Sc. University of Debrecen, Medical and Health Science Centre, Debrecen, Hungary (B.F.). fulesedi@med.unideb.hu

References

1. Pongrácz A, Szatmári S, Nemes R, Fülesdi B, Tassonyi E: Reversal of neuromuscular blockade with sugammadex at the reappearance of four twitches to train-of-four stimulation. Anesthesiology 2013; 119:36–42
2. Capron F, Alla F, Hottier C, Meistelman C, Fuchs-Buder T: Can acceleromyography detect low levels of residual paralysis? A probability approach to detect a mechanomyographic train-of-four ratio of 0.9. Anesthesiology 2004; 100:1119–24
3. Claudius C, Skovgaard LT, Viby-Mogensen J: Is the performance of acceleromyography improved with preload and normalization? A comparison with mechanomyography. Anesthesiology 2009; 110:1261–70
4. Kopman AF, Klewicka MM, Neuman GG: The relationship between acceleromyographic train-of-four fade and single twitch depression. Anesthesiology 2002; 96:583–7
5. McIntyre JA, Castaner J: Sugammadex sodium. Drugs Fut 2005; 30:780–4

(Accepted for publication October 21, 2013.)

Influence of Body Mass Index and Epidural Anesthesia on Lung Function

To the Editor:

I read with interest the report by Severgnini *et al.*[1] in which they describe that the protective mechanical ventilation improves postoperative pulmonary function in patients undergoing open abdominal surgery with general anesthesia. However, we wish to raise two concerns which may undermine the clinical validity of the authors' conclusions.

First, the authors state that the exclusion criteria included patients with body mass index greater than 40 kg/m^2. It means that the inclusion criteria included patients with body mass index 40 kg/m^2 or less, and obese patients (mildly obese: body mass index 25–30; obese: body mass index >30) were also included in this study. Obesity is a risk factor for perioperative pulmonary complications as the pathophysiological changes induced by obesity may jeopardize respiratory function and contribute to pulmonary morbidity, such as hypoxemia, hypercapnia, and atelectasis.[2] In addition, obesity is an important risk factor for perioperative impairment of spirometric