Sugammadex®: New Questions on Reversion

Sugammadex® recently launched in the Brazilian market is a modified gamma cyclodextrin that is showing favorable results on reverting the motor blockade especially that of rocuronium. One of the advantages of this agent over neostigmine is to allow reversion of relaxation when the patient is deeply curarized. However, when using Sugammadex® under this condition of deep blockade a phenomenon never observed before has been recorded: recovery of TOF (train-of-four) before complete recovery of T1 (single twitch) with a difference of up to 5 minutes between these two types of neurostimulation [1]. The concept of satisfactory recovery includes only the return of TOF > 0.9 or according to current recommendations, around 1 [2,3].

Monitoring of neuromuscular transmission (NMT) is different from other types of monitoring used in anesthesia, such as pulse oximetry, because there is the need of interpreting the data provided by the peripheral nerve stimulator.

For better understanding, it is possible to divide NMT phenomena in three distinct parts: pre-synaptic processes, those related to the synaptic cleft and basement membrane, and post-synaptic or muscular. In the first, greater prominence is given to the A α motor neuron in which neuronal nicotinic receptors can be identified [4], as well as voltage-gated calcium and potassium channels, which are fundamental structures to control the entry of calcium into the neuron. These receptors have particularities that differentiate them from muscular receptors, such as the presence of only two types of subunits, α 2-10 and β 2-4, and the absence of safety margin [4-8]. This last characteristic is related by a positive feedback mechanism from stimulation of α 3 β 2 nicotinic receptor to the additional release of acetylcholine in the presence of strong stimuli.

When the neuronal receptor is occupied by a non-depolarizing neuromuscular blocker (NMB) the positive feedback mechanism and the release of additional acetylcholine do not occur, and in the presence of a strong stimulus the muscle does not maintain an intense contraction, i.e., shows fatigue. Other mechanisms, besides the blockade of neuronal nicotinic receptors, seem to be involved with the development of fatigue according to what has been shown in muscle-phrenic nerve preparation. Among them are the facilitator action of type 1 muscarinic receptors (M1) and/or inhibitory action of type 2 (M2) [9]. In clinical monitoring this fatigue is characterized by a TOF < 0.9 [2,10,11].

Physiologically, acetylcholine molecules that were not destroyed in the synaptic cleft by acetylcholinesterase arrive at the muscular nicotinic receptor and occupy it triggering the opening of the receptor central pore. That is represented by M2-M4 chains situated in the transmembrane portion of the sarcolemma [4,8]. Hydrated sodium molecules enter through this pore generating the action potential. The electric potential stimulates voltage-gated sodium receptors juxtaposed to muscular nicotinic receptors that allow the additional entry of sodium magnifying the action potential. This membrane depolarization releases intracellular calcium molecules, which, on their turn, trigger muscle contraction. Muscle contraction or the post-synaptic mechanism is evaluated by the monitor by the response to the isolated stimulus, T1.

In the presence of a non-depolarizing NMB that competes with acetylcholine for the binding sites in muscular nicotinic receptors there is reduction in the muscle contraction represented by depression of T1, as long as the occupation surpasses the safety margin.

Succinylcholine the only depolarizing NMB used in clinical practice does not have affinity with neuronal nicotinic receptors in conventional doses and, therefore, fatigue is not observed in the monitor. Succinylcholine occupies post-synaptic receptors and decreases or abolishes muscle contraction, i.e., depresses or overturns T1.

The administration of elevated doses of Sugammadex® to antagonize deep blockades promptly recovers TOF and, therefore, "releases" neuronal nicotinic receptors of the steroidal NMB, more specifically rocuronium. However, contrary to neostigmine it does not promote reestablishment of T1 on the same proportion and speed, i.e., muscle receptors are still blocked by rocuronium. If we used the NMT monitor this response follows the pattern of a partial succinylcholine blockade, i.e., depression of T1 with maintenance of TOF.

After this evidence the following questions remain: is it possible to consider "complete reversion" of the NMB with depression of T1 present? Why the rapid decrease of rocuronium molecule first reverberates on neuronal receptors, the ones that do not have safety margin? Which are the effects of this drug that, on the NMT monitor, shows the same pattern of a partial blockade with succinylcholine? What is the clinical repercussion of this type of reversion?

Neuromuscular transmission is a complex mechanism that still goes without definitive answers. Many explanations have been obtained with animal studies in which genetic manipulation resulting in modified animal allows the understanding of particular aspects of nerves and muscles and their occupation by venoms or xenobiotics. We hope that with this "new" pattern of reversal after using Sugammadex® some concepts and mechanisms of action of NMBs on the NMT, as well as those related to reversion in anesthesiology will be reviewed.

Dra. Maria Cristina Simões de Almeida
Hospital Universitário
Universidade Federal de Santa Catarina

Dr. Giovani de Figueiredo Locks
Hospital Universitário
Universidade Federal de Santa Catarina