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DO WE NEED TO USE SUGAMMADEX AT THE END OF A GENERAL ANESTHESIA TO REVERSE THE ACTION OF NEUROMUSCULAR BLOKING AGENTS?

Position Paper on Sugammadex use

G. Della Rocca [1], P. Di Marco [2], L. Beretta[3], AR De Gaudio[4], C. Ori[5], P. Mastronardi[6]

on behalf of SIAARTI: Società Italiana di Anestesia, Analgesia, Rianimazione e Terapia Intensiva.

[1] Della Rocca Giorgio, Department of Anesthesia and Intensive Care Medicine. University of Udine. Udine, Italy

[2] Di Marco Pierangelo Department of Anesthesia and Intensive Care Medicine, "Sapienza" University of Rome. Rome, Italy

[3] Beretta Luigi - Associate Professor of Anesthesia and Intensive Care – Vita-Salute S. Raffaele University – Milan, Italy

[4] AR De Gaudio, Department of Anesthesia and Intensive Care Medicine. University of Florence. Florence, Italy.

[5] Ori Carlo, Department of Anesthesia and Intensive Care Medicine. University of Padua. Padua, Italy.

[6]Mastronardi Pasquale Department Surgery, Anesthesia, Intensive Care Medicine and Emergency "Giuseppe Zannini" , University of Napoli "Federico II", Napoli. Italy.

Address for correspondence:

G. Della Rocca, MD

Clinica Anestesia e Rianimazione

Padiglione Petracco - AOU Udine

P.le S. M. Misericordia, 15 - 33100 Udine, Italy

E-Mail: giorgio.dellarocca@uniud.it

Tel. +39 0432 559500-1

Fax. +39 0432 559512

Risultato controllo elenco partecipanti GdS

Sugammadex, the first selective relaxant-binding agent indicated to reverse the neuromuscular blockade induced during general anesthesia, was recently introduced into clinical practice. In the present report, the following issues pertinent to the use of sugammadex in anesthesia practice are discussed: the intraoperative use of NMBAs and the incidence of postoperative residual curarization (PORC); the efficacy and safety of rocuronium plus sugammadex compared to succinylcholine for rapid sequence induction; the availability of sugammadex in hospitals; and, finally, some relevant legal medical aspects.

The availability of sugammadex, considerably more expensive than neostigmine, depends on the following condition: strong agreement exists within the scientific field of anesthesia with regard to the safety and efficacy of sugammadex as a reversal agent of steroidal NMBAs; Neuro-Muscular Transmission Monitoring and PORC is a well documented problem in postoperative management. The incidence of PORC is under-estimated and the depending on risks are: weakness, postoperative inhalational events, hypoxemia, and pneumonia. Neuro-Muscular Transmission Monitoring is recommended to aid the selection of the appropriate NMBAs reversal drug and in order to monitor the recovery of neuromuscular function; clinical evaluation alone is not recommended practice. In the case of rapid sequence intubation (RSI), rocuronium (1.2 mg/Kg) administration followed by sugammadex represents a better choice in terms of efficacy and safety than succinylcholine. If the efficacy and safety of a new drug are superior to those of its predecessor, the better performing drug should be made openly available in hospitals. The absence of the superior agent should be the subject of patient information and this would create complains.

Key words:

Sugammadex, neuromuscular blocking agent, reversal, cost effectiveness.

Introduction

Before the introduction of neuromuscular muscular blocking agents (NMBAs) into the operation theatre, intravenous or inhalation agents alone were used to induce and maintain anesthesia. The deep inhalation of anesthetics was the only method available to ensure muscle relaxation and was thus routinely used despite the associated risk of respiratory or cardiac depression. Tracheal intubation was uncommon practice (1).

The capacity to induce muscle paralysis via the administration of NMBAs revolutionized the concept of general anesthesia, which became the harmonious combination of narcosis, analgesia and muscle relaxation, otherwise known as "balanced anesthesia", with each effect being induced through the action of different pharmacological agents (1, 2).

Muscle relaxants can be classified as depolarizers or non-depolarizers. Depolarizers exert their effect by depolarizing the end-plate via the stimulation of acetylcholine receptors present within the neuromuscular junction, causing muscle contraction and inducing paralysis. The prototypical depolarizer is suxamethonium, which is also the only depolarizer used in the clinical setting. Its onset of action is particularly fast, acting within 60 seconds, however its duration of action is short, at less than 5 minutes. The side-effects of Suxamethonium include malignant hyperpyrexia, increased intraocular pressure and life-threatening hyperkalemia and it is contraindicated in patients with burns or neuromuscular diseases, limiting its use in clinical practice (1).

Non-depolarizers, as the name indicates, do not depolarize the end-plate. Their onset of action is significantly slower (2-3 minutes) than that of suxamethonium, thus non-depolarizing NMBAs are not suitable for the rapid control of the airways. They exert their effect through the competitive antagonism of acetylcholine receptors within the neuromuscular junction. The action of non-depolarizers is reversed by anti-cholinesterases, such as neostigmine (2), which exert their effects at

both nicotinic and muscarinic receptors. Anti-cholinergic drugs, like atropine, are also given to counteract the side-effects induced by the anti-cholinesterase, such as bradycardia; however, their use provoke other adverse events, like blurred vision, a dry mouth, and tachycardia (3). In addition to pharmacodynamic aspects, other factors influence the degree of reversal, such as:

a) the timing of anti-cholinesterase administration;

b) the dose of anti-cholinesterase;

c) concomitant medications;

d) electrolyte abnormalities;

e) coexisting diseases: in particular, hepatic and/or renal disease (3).

Post-anesthetic morbidity associated with incomplete reversal of neuromuscular blockers, defined as Post-Operative Residual Curarization (PORC), is still a frequent occurrence (4). Despite the routine administration of neostigmine as a reversal agent for non-depolarizing NMBAs, the incidence of critical respiratory events in the postoperative care unit (PACU) is at least 0.8% (5,6), thus representing a significant problem.

The significant side-effects and limitations of the currently available neuromuscular blocking agents mean that the debate over their use remains actively open and the search for the ideal drug continues.

The drug **sugammadex** was recently introduced into clinical practice. Sugammadex is the first selective relaxant-binding agent shown to reverse the neuromuscular blockade induced during general anesthesia (5). Sugammadex does not exert its effect via acetylcholinesterases, removing the need for anti-cholinergic drugs and their aforementioned adverse side-effects. Rather, its unique mechanism of action involves the encapsulation of the NMBAs, which effectively lowers the concentration of NMBAs and, in turn, reduces its effect within the neuromuscular junction.

Furthermore, as reversal by sugammadex is independent of the depth of neuromuscular block or the degree of spontaneous recovery, reversal can be induced and accomplished even during profound neuromuscular block (3,6). This has an important implication as it means that the morbidity associated with **residual postoperative neuromuscular blockade** could be significantly decreased. Moreover, access to a drug like sugammadex would mean that high doses of a non-depolarizing blocker, like rocuronium or vecuronium, could be used as a safe approach for the **rapid control of the airways** prior to tracheal intubation. The availability of sugammadex paradoxically represents a life-treating therapy for patients in the "cannot-ventilate/cannot-intubate" clinical scenario (5).

In this position paper, the following issues will be discussed:

- the modulation of the intraoperative use of NMBAs and the problem of postoperative residual neuromuscular blockade, defined as PORC;
- the efficacy and safety of the use of rocuronium plus sugammadex *vs.* succinylcholine for rapid sequence induction (RSI);
- the availability of sugammadex in hospitals, as a therapeutic option and/or standard of care, and legal medical aspects.

INTRAOPERATIVE USE OF NMBAs AND POSTOPERATIVE RESIDUAL CURARIZATION

Curarization is a cornerstone of general anesthesia, facilitating intubation, patient immobilization and surgical approaches; in particular, its use has become mandatory for abdominal and laparoscopic surgery. The risk related to the use of curarization has been reduced over the years due to the introduction of second- and third-generation (NMBAs) and neuromuscular monitoring devices. Despite these advances, residual neuromuscular blockade remains a common and often undetected problem after surgery, leading the way to patient complications; the rates of such complications exhibit a high range of variability because confounding factors are present (6,8,9).

In the Risultato controllo elenco partecipanti GdS using the Train of Four (TOF) technique, emergence from neuromuscular block was estimated to be safe with a TOF ratio (TOF_R) > 0.7. More recently, however, studies which take into consideration more appropriate clinical evaluations (e.g. the ability to swallow) have shown that neuromuscular block can still be present with a TOF_R > 0.9 (10). In the absence of monitoring, clinical signs obtained after emergence (such as tidal volume, vital capacity, normal values of end-tidal carbon dioxide, the ability to generate a negative inspiratory pressure > 30-50 cm H_2O, the ability to maintain the head erect for at least 5 seconds, and the ability to hold an object between the teeth against a force whilst trying to pull it out) are not sensitive enough indicators (9).

Respiratory impairment is the most common complication of postoperative residual paralysis (PORC) since incomplete neuromuscular recovery only affects certain groups of muscles, such as those of the upper airways, the pharynx, and the proximal esophageal sphincters. The upshots of such complications include delayed discharge from the Post Anesthesia Care Unit (PACU), longer extubation times, hypoxia, aspiration, and, in severe cases, pneumonia (9).

The extensive use of neuromuscular monitoring, the correct type and dosage of NMBAs, and the administration of reversal agents can significantly reduce the incidence of postoperative residual paralysis. Sugammadex is able to completely and rapidly (2-3 min) reverse the neuromuscular block induced by rocuronium and vecuronium and is not associated with any cholinergic side effects (4,11).

THE EFFICACY AND SAFETY OF ROCURONIUM PLUS SUGAMMADEX *VS.* SUCCINYLCHOLINE FOR RAPID SEQUENCE INDUCTION

No drug in anesthesia is as problematic as succinylcholine considering the number and seriousness of its associated side-effects. Nevertheless, very few drugs have been used for such a long time (60 years since its introduction in 1951). For decades researchers have searched for valid alternatives to succinylcholine, yet the drug is still being used in large numbers of patients all over the world. Two

main advantages favor the use of succinylcholine: its early onset and early offset. Over the last twenty years, its clinical use has been restricted to procedures requiring a deep but short neuromuscular blockade (12). Even its use to facilitate tracheal intubation is becoming more and more controversial and disputed, yet many Anesthesiologists still deem it to be the best choice for an unexpected difficult airway, and are convinced that spontaneous breathing can be recovered quickly before hypoxemia sets in. However, this common conviction is utterly incorrect: following the administration of succinylcholine, SpO_2 desaturation occurs before the mean spontaneous breathing recovery time, even in properly pre-oxygenated patients (13). Moreover, a low metabolic rate (whether it be acquired or genetically inherent) can delay the succinylcholine offset time, and at the same time oxygen consumption due to fasciculations leads to faster SpO_2 desaturation (14).

Succinylcholine has always been the drug of choice for rapid sequence intubation (RSI) due to onset/offset timing and intubation conditions (15). However, the introduction of rocuronium (NMBAs) and sugammadex (NMBAs reversal agent) has changed this scenario: rocuronium (1.2 mg/kg) administration is able to ensure an even faster onset and an easier tracheal intubation than succinylcholine, while sugammadex (16 mg/kg) allows a quicker recovery from deep neuromuscular block. The latest confirmation was provided by Sorensen et al. (16), who compared succinylcholine to rocuronium/sugammadex treatments, and described no difference in intubation time, but a significantly shorter time of spontaneous breathing recovery for the latter: 400 seconds *vs*. 216 seconds, respectively.

What is sure is that a full dose of rocuronium (1.2 mg/kg) is at least as good as succinylcholine in terms of intubation timing and conditions, while a dose of sugammadex of 2 to 16 mg/kg leads to faster spontaneous breathing recovery than can be achieved with succinylcholine Recently, even a dose of 1.0 mg/kg of the rocuronium (plus sugammadex sequence) was shown to have a significantly quicker offset of neuromuscular block compared with that achieved with succinylcholine (16), while intubation conditions and time to tracheal intubation were non significantly different.

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After decades of research aimed at finding a single drug that performs better than succinylcholine, the synergy of two different drugs (rocuronium and sugammadex) has to be finally accepted as a better choice than succinylcholine in terms of both efficacy and safety.

THE AVAILABILITY OF SUGAMMADEX IN HOSPITALS AND LEGAL MEDICAL ASPECTS.

The efficacy and safety of sugammadex and the myths and facts prevailing in neuromuscular pharmacology have been discussed above and reported in more depth elsewhere (4).

Now, let us consider the scenario whereby an anesthesiologist judges that the use of sugammadex could significantly reduce the perioperative risk in a specific patient, but the drug, although approved for use in the residing country, is not made available by the Regional Council or by the specific hospital in question. How should the anesthesiologist behave? Who will be deemed responsible if the patient experiences any damage which could have been prevented by the use of Sugammadex?

It may be useful to recall what was recently declared by the “Italian Cassazione Civile” (the Supreme Court, i.e. the highest court in the Italian Judicial System) (Judgment n. 15386, 13 July 2011) regarding the physician’s obligation to inform. The case faced by the Supreme Court stemmed from a claim brought against a physician expert in ultrasound imaging by the parents of a child born with severe malformations that were not diagnosed prenatally. In the I and II grade judgments, the claim was rejected because, according to the lower courts, the misdiagnosis of the sonographer was not to be referred to an inadequacy of his professional conduct, but rather to the intrinsic limitations of the devices made available to him. The Supreme Court, however, upheld the claim of the parents because, in the opinion of the judges, the physician was obliged to inform the patient about the possibility of using a center with a higher level of specialization, pointing out that that is "the responsibility of the health care provider, as he is howsoever required to inform about the potential unsuitability of the equipment used". This same principle could be extended to the duty to inform the patient about the existence of centers that are not necessarily more specialized,

but that nonetheless have access to more adequate drugs. Thus it would appear that it may be considered the responsibility of an Anesthesiologist to inform patients facing elective operations when sugammadex is not among the drugs to which the Anesthesiologists of that hospital have access and to indicate the other hospitals within or outside the region where the patient can expect a safer anesthetic assistance due to the availability of a drug able to reduce the risk of serious consequences that are objectively predictable and preventable.

We can further hypothesize that Anesthesiologists might also be made liable for injuries caused to patients cared for in urgent/emergent scenarios. Let us consider the event of an emergency situation where an expected difficult intubation and ventilation is associated with the impossibility to use succinylcholine (for example, in the field rescue of a patient with extensive third degree burns involving neck and face) and the use of NMBAs is still necessary. In the case of serious or fatal complications arising from the difficult intubation, there might be grounds to place responsibility upon the hospital and the Region Council that did not provide access to a drug that would have permitted the use of a non-depolarizing NMBAs and, if necessary, the rapid resolution of the block itself, allowing the recovery of spontaneous breathing before an environment is reached where devices adequate to deal with a difficult intubation, like a fiberscope, were available.

Statement 1: agreement on sugammadex efficacy and safety.
Strong agreement exists within the scientific field of anesthesia with regard to the safety and efficacy of sugammadex as a reversal agent of steroidal NMBAs.

Statement 2: Neuro-Muscular Transmission Monitoring and PORC.
The incidence of PORC is under-estimated and the depending on risks are: weakness, postoperative inhalational events, hypoxemia, and pneumonia. Neuro-Muscular Transmission Monitoring is recommended to aid the selection of the appropriate NMBAs reversal drug and in order to monitor the recovery of neuromuscular function; clinical evaluation alone is not recommended.

Statement 3: Rocuronium plus Sugammadex *vs*. succinylcholine.
In the case of RSI, rocuronium (1.2 mg/Kg) administration followed by sugammadex represents a better choice in terms of efficacy and safety than succinylcholine.

Statement 4: Legal medical aspects.

If the efficacy and safety of a new drug are superior to those of its predecessor, the better performing drug should be made openly available in hospitals. The absence of the superior agent should be the subject of patient information and this would create complains.

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