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Essay

Strategies to Reduce the Most Frequent Adverse Events of Neuromuscular Blocking Agents

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ABSTRACT

Neuromuscular blocking agents are without doubt the drugs most frequently associated with perioperative adverse events in anesthesia. Acknowledging and treating those patients at high risk of developing unexpected events caused by the administration of these agents should become a routine for the perioperative medicine specialist. This article is a reflection on simple pharmacokinetics and pharmacodynamics for improved safety in the administration of NMBs by the anesthesiologist. Preserving internal homeostasis, thermoprotection and securing microcirculation are key strategies for reducing events such as postoperative residual curarization. Furthermore, a right clinical approach to patients at high risk of developing NMB-related hypersensitivity reactions enables a safe and comprehensive management of the patient, avoiding subsequent and more severe or even fatal events.

Estrategias para disminuir los eventos adversos más frecuentes relacionados con bloqueadores neuromusculares

Palabras clave:
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RESUMEN

Los bloqueadores neuromusculares (BNM) son, sin duda, los medicamentos más asociados a eventos adversos perioperatorios con que debe lidiar el anestesiólogo. Reconocer y tratar a los pacientes con alto riesgo de eventos inesperados relacionados con la aplicación de estos medicamentos debe convertirse en una rutina para el especialista en medicina perioperatoria. Este artículo de reflexión plantea sencillos conceptos de farmacocinética y farmacodinámica que permiten al anestesiólogo hacer más segura la administración de BNM. La preservación de la homeostasis interna, la termoprotección y asegurar la microcirculación son estrategias básicas para disminuir eventos como la curarización residual postoperatoria. Por otra parte, un adecuado enfoque clínico para pacientes en riesgo de reacciones de hipersensibilidad a BNM permite brindarles un manejo seguro e integral, previniendo posteriores eventos de mayor severidad o incluso fatales.

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Neuromuscular blocking agents (NMBs) have been part and parcel of our clinical practice since the early 40's.[1,2]. It has been acknowledged since then that in addition to the clinical benefits, these agents may have severe implications for the perioperative outcome, particularly in ambulatory surgery. Though not exclusively, postoperative residual curarization and allergic reactions are the two most important events associated with the use of these drugs.

Preventing a prolonged neuromuscular blockade

Postoperative residual curarization (PORC) is certainly the most frequent complication associated to the use of NMBs. Various clinical conditions may be identified that as a whole, increase the risk of developing PORC. Hypothermia is the number one factor associated with a lower muscle cell heat generation and altered ionic conductance. NMBs association with hypoperfusion and tissue acidosis makes them an independent marker for POCR in critical patients.[3]

Age is associated with loss of muscle mass and hence with the loss of available nicotinic receptors, resulting in changes in the pharmacodynamics of NMBs in variable degrees, particularly steroids. In addition to the conditions related to the affinity of these quaternary ammonia, any change in the proportion of available receptors/drug concentration at the biophase, significantly affects the clinical outcome. Moreover, the progressive decrease of the volumes of distribution notably alters the pharmacokinetics of NMBs, particularly when combined with impaired hepatic and renal metabolism and excretion in the elderly. A trial by Kocabas et al,[4] found that old age and renal failure combined, severely affected the prolongation of the effect of an NMB frequently used in our clinical practice.

There are several risk factors for PORC, such as those directly associated with NMBs, i.e.: pharmacological reversal, drug interactions with calcium antagonists and aminoglycosides, clinical conditions such as renal failure and chronic systemic diseases, as well as particular biometric conditions of the patient (table 1).

The work by Debaene et al was quite revealing and alerted against the high incidence of TOF ratios below 0.9 in patients receiving a single dose corresponding to $2\times DE_{95}$ of a non-depolarizing "intermediate duration of action" NMB, even 100 minutes following its administration.[5] More interesting yet was the finding that clinical evaluations such as head lift and "tongue depressor" tests were similar in terms of sensitivity to more objective tests such as TOF and DBS stimulus response, but with lower specificity (87% vs. 99%), a key indicator we should not overlook. Subsequent studies showed that PORC was not the only frequent event with direct influence on the patient's length of stay in the recovery room[6] and that there was a misperception by physicians about the danger of this particular event.[7,8]

The time of administration and the neostigmine doses used for NMB reversal are usually controversial; however, the initial reports on NMBs-related side effects have traditionally limited their routine use. A meta-analysis by Tramèr and Fuchs-Buder showed a linear relationship between the neostigmine dose and the incidence of postoperative nausea and vomiting when the dose administered exceeds 2.5 mg but this was not the case when lower doses were used (1.5-2 mg).[9] It has been recently emphasized that the administration of neostigmine should be different in patients receiving TIVA versus patients receiving halogenated agents. The study groups recommend that the 4 responses to the TOF stimulus when using halogenated anesthesia should be present, as opposed to the usual criterion of >2 responses.

If neostigmine is an incomplete solution to the problem, what else can we do to try to prevent PORC? Trying to measure the functional recovery of the neuromuscular junction sounds interesting; however, the evidence has been discouraging. The meta-analysis by Naguib et al[10] did not find a significant difference when using neuromuscular blockade monitoring; however, this observation may proof difficult to interpret when considering the heterogeneity of the studies included in the analysis. The introduction of cyclodextrins opened a wide door in terms of safety and the NMBs antagonistic mechanism. Cyclodextrins have proven their effectiveness as an alternative to reversal therapy under normal conditions, and have been helpful in recovering from profound neuromuscular blockade.[11] There are already some publications discussing the use of cyclodextrins in the management of severe rocuronium-induced anaphylaxis.[12,13]

On he basis of the above, the message regarding some recommendations to avoid PORC when using NMB is very clear:

- Use quantitative neuromuscular function monitors and be as objective as possible when considering the possibility of PORC.
- Assess the need for neostigmine NMB reversal at least 20 minutes before awakening. Make sure that the maximum effect time has elapsed prior to extubation.
- If your patient received halogenated agents, wait until the 4 TOF responses show up before reversing with neostigmine.
- Moderate doses of neostigmine (20-35 µg/kg) do not increase the incidence of nausea and vomiting. Raising the dose above 40 µg/kg does not improve the result of the reversal.

Table 1 – Risk factors for postoperative residual curarization.

Types	Specific situations
NMB-related	Additional NMB doses High doses
Related to pharmacological reversal	Administration too close to awakening Inadequate dosing
Drug interactions	Calcium antagonists Aminoglycosides, clindamycin
Clinical conditions	Cirrhosis of the liver Chronic renal failure Chronic systemic disease State of muscular deconditioning
Biometric conditions	Short size Elderly Female

Source: authors.

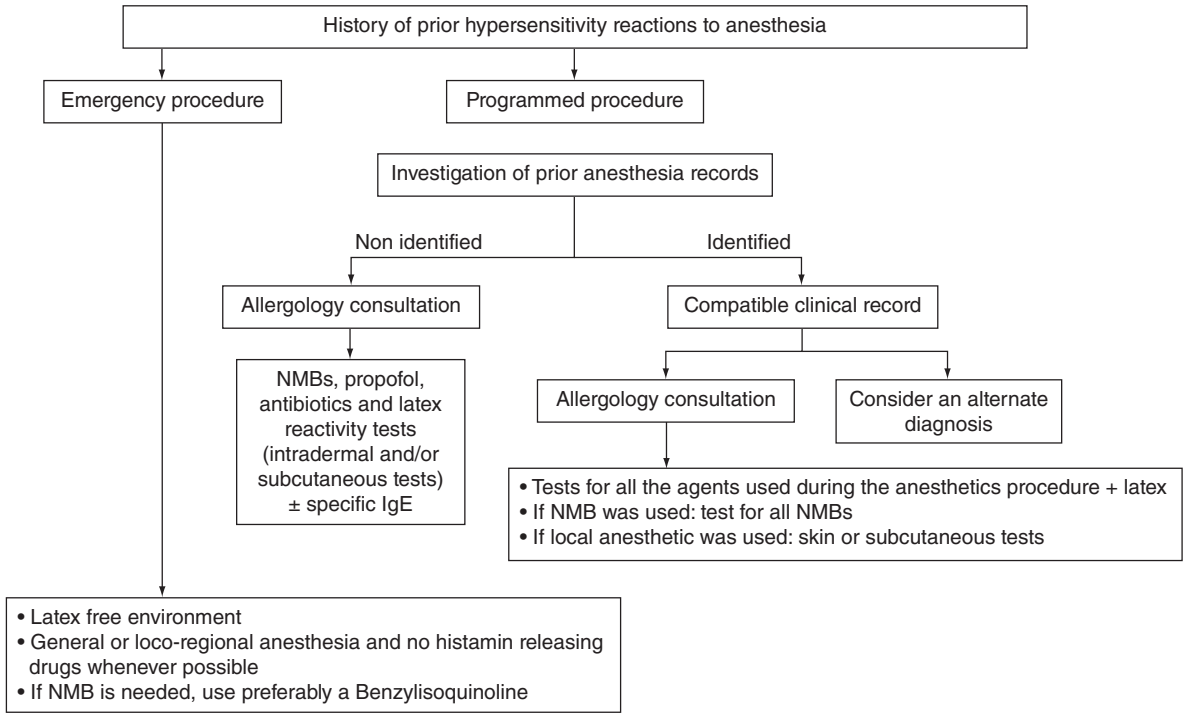

Fig. 1 – Decision algorithm for patients with a high risk of hypersensitivity events to NMB and other drugs frequently used during surgery under anesthesia. Adapted from Mertes PM et al. Reducing the risk of anaphylaxis during anaesthesia: guidelines for clinical practice. J Invest Allergol Clin Immunol JIACI 2005;15(2): 91-101. (Reproduced with authorization). NMB: neuromuscular blocking agents.

- Long-acting NMBs are increasingly being used for specific situations. This is the age of "fast-track" surgery, which is beyond the scope of these drugs.
- When using steroidal NMBs avoid a profound neuromuscular blockade (<1 response to TOF stimulus) and consider reversal if consecutive doses have been used.
- Consider the use of amino acid-enriched solutions or cyclodextrins if the neuromuscular blockade is profound at the end of surgery; the benefits of early extubation outweigh the additional costs of this event.

Neuromuscular blocking agents (NMB) allergic reactions: how to anticipate and tackle them

Following the first reports on NMB allergic reactions in countries such as France, New Zealand and the UK, the active participation of the anesthesiologists has been encouraged to identify patients at high risk of developing adverse events.[14] NMB hypersensitivity reactions may be classified into two large groups: the immune or anaphylactic reactions (IgE mediated) and those associated with a direct histamine release (anaphylactoid). The usual clinical presentation of the former is bronchospasm associated with hypotension and shock, while the latter usually exhibit cutaneous manifestations. Despite a low incidence (1 in 10.000-20.000 cases), NMBs account for 50 to 70% of all anaphylactic events during surgery, over and above latex, antibiotics and colloids (approx. 10% of all anesthesia related complications).[15]

The identification of patients with prior hypersensitivity events during surgery is crucial because of an apparent association with the time of administration of the NMB (fig. 1). When considering other surgical procedures under anesthesia, these patients must be previously evaluated by an allergist who should identify the need for "delayed" testing including some skin (intradermal and inoculate) tests or specific IgE tests (radio immune absorbance tests [RIA], RAST, CAP-RAST) aimed at confirming the specific hypersensitivity to these drugs in anticipation of any future exposure.[5] For *de novo* cases in patients with a sudden episode of bronchospasm, difficult to manage sustained hypotension or skin reactions, the investigation of a probable relationship between the allergic event and any drug (including NMBs) requires measuring histamine levels within the first hour (sensitivity 75%; specificity 51%) and the measurement of serum triptases (sensitivity 64%; specificity 89%) if more than one hour has elapsed but less than 6. Outside this time range, the investigation of a probable related allergen should be postponed for several weeks following the stabilization phase, using delayed testing.

The management of NMB hypersensitivity reactions is no different from the usual management with any other drug.

Unfortunately, these episodes are sudden and unpredictable but in many cases severe enough to be life threatening. The success of the treatment is directly related to the early diagnosis of the condition. In 2005, an expert consensus developed some clinical guidelines for patients with immediate hypersensitivity reactions in the course of the anesthesia, or with a history of similar events. The consensus highlighted the value of a pre-anesthesia allergy investigation in these patients, the poor evidence regarding the value of premedication with steroids and/or H_2 antagonists, the usefulness of epinephrine administered through different routes and its association with extensive circulatory volume replacement and the optimization of mechanical ventilation using spray bronchodilators and corticosteroids in the event of an acute episode.[16]

There are other NMB-related adverse events such as malignant hyperthermia, neuromuscular injury and autonomic nervous system dysfunction, which are all beyond the scope of this analysis and deserve more extensive future discussion. We have tried to review the key concepts for two of the most frequent NMB-related adverse events: PORC and hypersensitivity reactions. The proactive role of the anesthesiologist in these two circumstances results in a safer and more comfortable practice for the patient; however, it requires an in depth knowledge of the pathophysiological mechanisms and underlying conditions for a timely identification and treatment of the patient.

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Conflict of interests

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