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Mini Review

Should we Change the Nomenclature of Neuromuscular Blocking Drugs?

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Abstract

Neuromuscular blocking drugs are not anesthetic drugs by themselves. However, neuromuscular blocking drugs are now used in about more than 90% of operations, to make anesthesia more perfect and optimal. But there is a problem in the terminology of these drugs with to some extent a controversy. So many anesthesiology articles, books, and anesthesiologists in their clinical practice are using the term neuromuscular blocking drugs for rapid-acting suxamethonium as well as other long-acting neuromuscular blocking drugs such for instance pancuronium, atracurium, rocuronium, et set. My idea here is about the terminology rather than the mechanism of action or clinical application.

Keywords: *Neuromuscular Blocking Drugs; Suxamethonium; Long Acting Drugs*

Introduction

At the beginning of anesthetic practice and precisely in the inhalational anesthetic era, the inhalational anesthetic agents were the only agents available at that time. The anesthesiologist was having no many choices, and they were obliged to use those agents to achieve all anesthesia requirements. Inhalational anesthetics were very effective agents, but they were offering nearly only one anesthesia aim which is the central nervous system depression. Anyhow, with progression in anesthetic practice, the IV anesthetic agents have appeared in addition to the analgesic agents (commonly opioids) and therefore nearly all aims of anesthesia begin to be fulfilled (CNS depression, amnesia, and analgesia). However, there was still a very important aim which was couldn't be achieved, that is offering muscle relaxation. At that time the patient even he was deeply anesthetized but he was still breathing spontaneously and intact muscle activity, and however, in attempts to offers a good muscle relaxation for surgery, the doses of inhalational drugs or other anesthetics must, therefore, be administered in high doses which may make the respiration so much depressed and even the patient may be jeopardized, and be in a very high-risk situation (cardiorespiratory depression). Anyhow, a time came that the muscle relaxant agents were discovered, studded, and applied clinically successfully, and so a revolution had occurred in anesthesia and we can say that a new anesthetic era was begun. It is of great importance to note that the neuromuscular blocking drugs are not anesthetic agents. They are not a CNS depressant, and not ever an analgesic drug but even so it offers a very much to anesthesia. However, these agents are included under the term of an anesthetic drug hypothetically. Even they are not anesthetic drugs, but they aid greatly in the advances in anesthesiology, as they are opening a gate for a very high number of researches and studies (Figure 1 and 2). Neuromuscular drugs therefore with other anesthetic agents offer balanced anesthesia that is CNS depression (unconsciousness), analgesia, and muscle relaxation.

Mechanism of neuromuscular relaxation

The classical description of the effect of the nondepolarizing neuromuscular blocking agents is that of competitive antagonism. The antagonist (nondepolarizing neuromuscular blocking drug) competes with the agonist (nicotinic acetylcholine) for the binding sites on the post-synaptic receptors (cholinoceptors) and the proportion of receptors occupied by acetylcholine or neuromuscular blocking drugs is determined therefore by their concentrations and affinities for the receptors. The higher the concentration of muscle relaxants in the synaptic cleft, relative to the concentration of acetylcholine, the more receptor sites are occupied by the neuromuscular blocking drugs, and the deeper is the neuromuscular blockade and vies versa (Figure 3 and 4) [1-3].

Regarding the depolarizing relaxants the binding to neuromuscular receptors with a short time molecule like ligand acetylcholine for activation of receptor usually needing 2 molecules. This about the ligand but for instance, the decamethonium (family of suxamethonium) has a straight-line confirmation, will mostly span the two neuromuscular nicotinic receptor sites. However, the longer molecules must

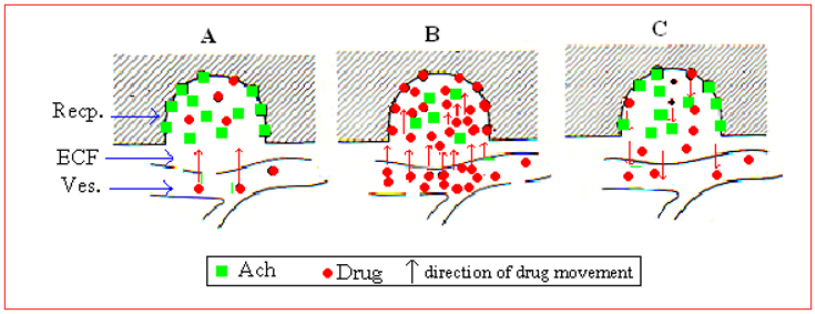

Figure 1: *A) Drug molecules are low concentration so the ligand giving action. B) The concentration of the drug is increased so repelling the ligand and giving its action. C) The concentration of the drug is decreased so the ligand resuming its action.*

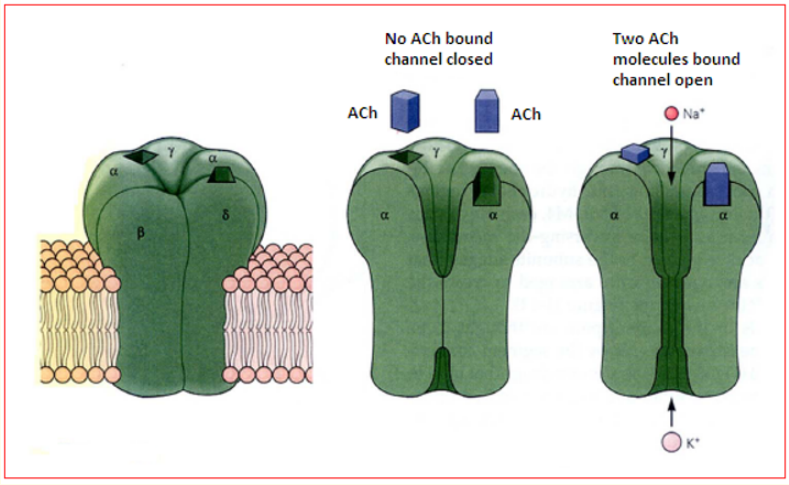

Figure 2: *Acetylcholine binds to the α subunits of the acetylcholine receptors.*

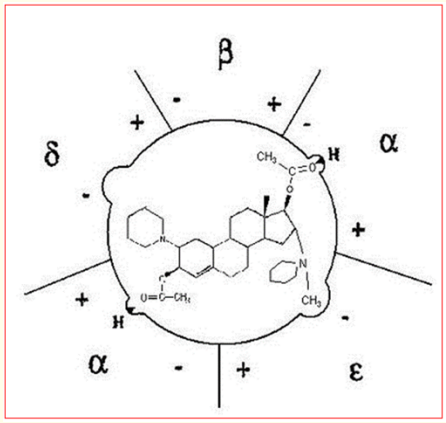

Figure 3: *A simple illustration of how vecuronium binds to the nicotinic receptor. Its D-ring binds to the receptor at two points and the lipophilic side of the molecule repels cations from flowing through the ion-channel. Note that the molecule binding the both α H site of the receptor.*

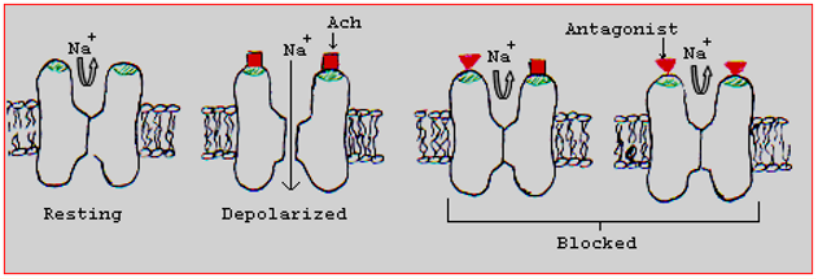

Figure 4: *The mechanism of blocking the neuromuscular nicotinic receptor by the antagonist (nondepolarizing block).*

bended to fitting the receptor sites (Figure 5). Regarding suxamethonium (succinylcholine) it has 10 carbon atoms between its N atoms (like decamethonium) but it was found that unlike decamethonium there must be 2 molecules (like in the case of acetylcholine) to open the neuromuscular receptor. The conformational explanation that each acetylcholine moiety of suxamethonium has a bent state. In this state, the N-N distance is shorter than the optimal distance for 10 carbon atoms and too short to occupy both receptor sites.

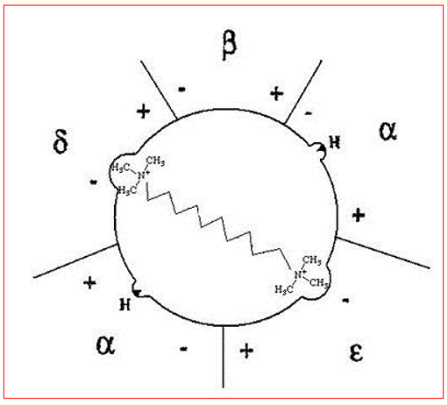

Figure 5: *Depolarizing drugs having a straight-line confirmation, so it is likely to span the two receptive sites with one molecule. Note that the molecule binding the δ and ε sites of the receptor (See figure 3).*

Sometimes the suxamethonium may lead to a clinical state called the dual block. If suxamethonium remains at the neuromuscular junction for an extended period [either because of a prolonged infusion in patients with normal plasma cholinesterase activity or because a normal or relatively overdose has been given to a patient with a low level of plasma cholinesterase] the characteristics of the block herein will be changed. The membrane potential will gradually recover to a normal state (though the neuromuscular transmission is still blocked). In this time surprisingly the original depolarizing block will change over to a nondepolarizing-like block (characterized by tetanic fade, post-tetanic facilitation, and fade in the train of four responses). This change or transition in block characteristics has been described as a change from a phase I to phase II block. There are other less useable nomenclatures may be dealt with in such condition, such as [dual block, mixed block, or desensitization block]. The term desensitization block particularly should not be used to indicate the phase II block, because it is not proved that desensitization may occur in this condition.

Regarding the repeated use complications of neuromuscular blocking drugs, there this no problem with giving the long-acting neuromuscular blocking drugs in frequent and repeated administration of them, but the short-acting drugs suxamethonium its repeat administration may lead to complications like the dual block, hyperkalemia, and prolong relaxation which cannot be reversed by using neostigmine like in case of using the long-acting drugs.

My theory of nomenclature

After practicing anesthesiology for about 35 years my idea is: commonly the neuromuscular blocking drugs are classified as:

1. Depolarizing neuromuscular blocking drugs.
2. Nondepolarizing neuromuscular blocking drugs.

Really, regarding the mechanism of action of these drugs, this classification and nomenclature are being to some extent incorrect. Regarding the nondepolarizing neuromuscular blocking drugs there will be a certain way that the drug is blocking (closing) the ionic channel of the nicotinic receptor and by closing the receptor [blocked] no ion exchange will occur and no action potential will be initiated and progressed, leading the muscle to be relaxed. However, when dealing with depolarizing drugs, their action on the neuromuscular nicotinic receptor is differing completely, as these drugs seem to depolarize the receptor making it opened like the ligand acetylcholine, and ion exchange will occur but as the action of depolarizing drugs is much longer than the ligand (minutes versus milliseconds) then some type of no ion exchange will further occur [equilibration or inactivation of voltage-gated sodium channels] the condition indeed some call it [desensitization, when equilibration of ions occur then no further action potential will be initiated and the muscle, therefore, relax not because of the block but instead because of prolonged receptor state of opening (a state like opened lazy receptor) or (the persistent depolarization makes the receptor resistant to further stimulation by acetylcholine)]. In this case depolarizing drugs cannot consider as blocking drugs, rather than like if the acetylcholine prolonged its action. Therefore, I believe it is more logical and accurate to change the classification of neuromuscular blocking drugs as follow:

1. Depolarizing neuromuscular relaxing [non-blocking] drugs.
2. Nondepolarizing neuromuscular blocking drugs.

Conclusion

From the above discussion, it clears that there is some wrong in the terminology regarding the neuromuscular blocking drugs, besides I don't prefer using the term muscle relaxants as there are other medications that may be used to relax the muscles but cannot to be applied in anesthesiologic practice. Finally, I believe to rereview and discuss using the right term for each group of drugs that belong to the same pharmacological family (group). But here I concern the anesthesiologic drugs as it is our specialty.

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