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Factors affect neuromuscular transmission and block

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Introduction

There are many factors that may affect the normal physiological neuronal and neuromuscular endplate electrochemical transmission (both stimulation and depression). Also there are many factors that may change the ability and characteristics of neuromuscular blockade that produced by neuromuscular blocking drugs. This chapter will deal and discussing these factors in general.

Temperature

Effect of temperature on neuromuscular transmission: The mechanism by which the change of temperature is altering the neuromuscular transmission is really complex. Changes of temperature may influence events that taking place in the motor nerve, in the synaptic cleft, in the endplate and in the muscle. A decrease in temperature (hypothermia) may causes:

a. A decrease in conduction along the nerve, but in sometimes causing an increase in evoked release of acetylcholine from the motor nerve terminal. The velocity of nerve conduction is delayed approximately 2 m/sec/ºC reduction in temperature in the temperature range of 36-26ºC but block of nerve impulses does not occur. Numerous processes are involved when transmitter is released from the nerve terminal. The maximum transmitter release at approximately 20-25ºC is related to temperature-dependent rate of calcium ion removal from its intracellular active site.

b. In the synaptic cleft a fall in temperature reduce the activity of acetyl cholinesterase, thereby increasing the concentration of acetylcholine.

c. Post-synaptic receptors sensitivity increases with decreasing temperature. However, the resting membrane potential, endplate membrane threshold for initiation of a propagated action potential, endplate sensitivity to antagonists and acetyl cholinesterase activity are not significantly influenced by hypothermia.

d. A fall in temperature may cause depolarization of the endplate and a prolongation of the repolarization phase.

These changes are however, normally of little clinical significance, because of the marked margin of safety of the neuromuscular junction. More important is probably the effect of temperature on the muscle contraction itself. The type of muscle fibers in the muscle bulk is commonly having important influences on the muscle response. The response of the predominately slow twitch red and fast twitch white muscles increases in response to cooling.

In clinical practice the twitch tension of the adductor polices muscle decrease with fall in muscle temperature. A close relation between central body and adductor pollicis temperature is proved, with a temperature difference of 0.5-1ºC between them (Figure 1). It is found that peripheral cooling of the skin to 27ºC was associated with a decrease in the first response in TOF of 3-4% per each ºC and in the TOF ratio of 1% per each ºC (Figure 2). In connection with central cooling the twitch tension may decrease even more from 14 -20% per ºC. It is therefore essential to keep both core and peripheral temperature as near normal as possible when monitoring the neuromuscular function.

Muscle strength is reduced during hypothermia, both in the presence and in the absence of neuromuscular blocking drugs. A 2ºC reduction in body temperature may double the duration of neuromuscular blockade. A reduction in muscle strength must be expected at a body temperature less than 36ºC. Local cooling of the hand may make adductor pollicis twitch tension monitoring less useful during clinical anesthesia.

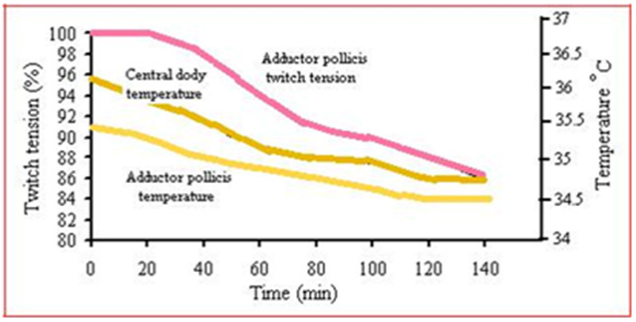

Figure 1 Simultaneous recording of the changes in central body and adductor pollicis muscle temperature and adductor pollicis twitch tension during central body cooling in the absence of neuromuscular blocking drugs.

Effect of temperature on the action of neuromuscular blocking agents: Intraoperative hypothermia due to decreased metabolic heat production, increased heat loss and reduced compensatory responses is common. A body temperature less than 35ºC is frequently encountered. During the past years a several investigations have shown that changes in body temperature influence the effect of neuromuscular blocking drugs. Despite the introduction of nerve stimulators that monitor neuromuscular function during surgery, residual paralysis at the end of anesthesia still occurs frequently and intraoperative hypothermia is a contributing factor to this adverse effect.

This subject is controversial, and the effect of temperature on the potencies of neuromuscular blocking agents remains unclear. All

researchers are not agreed about the effect of temperature on muscle relaxant action. Studies have shown conflicting results:

A. Hypothermia has been found to increase or decrease the effect of tubocurarine.

B. Hypothermia either increases or has no effect on pancuronium.

C. Hypothermia increase the paralysis produced by suxamethonium.

D. Hypothermia significantly prolonged the effect of the steroidal neuromuscular blocking agents.

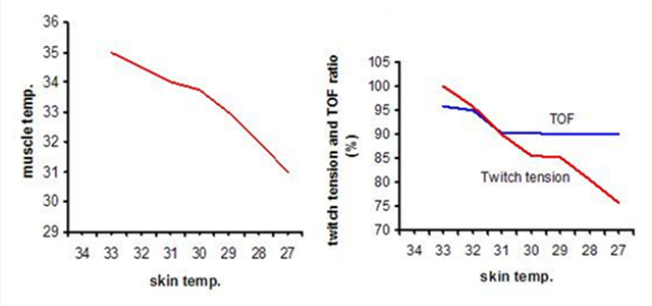

Figure 2 Peripheral cooling of the skin to 27°C was associated with a decrease in the first response in TOF of 3 - 4% per each °C and in the TOF ratio of 1% per each °C.

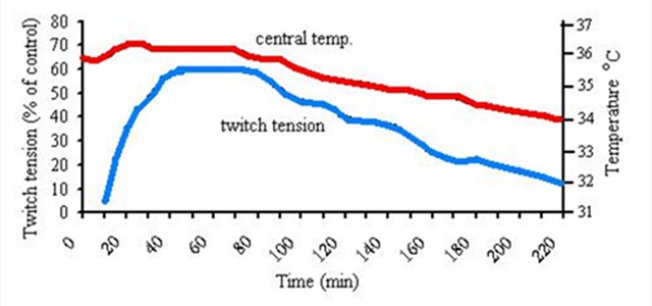

Figure 3 Where the central body temperature is allowed to decrease gradually from 36.5°C to 34°C, the twitch response decreased 20% per °C reduction in muscle temperature during a constant infusion rate of neuromuscular blocking drugs.

These variable results have many causes as the changes in temperature besides affecting virtually all processes involved in neuromuscular transmission and muscle contraction, may also affect, the pharmacokinetics of the muscle relaxants, blood flow, potassium ion concentration, and catecholamine levels. Therefore anesthetist should expect a prolongation effect of all commonly used neuromuscular blocking agents following a significant drop in temperature. Anyhow, the Arrhenius hypothesis suggests that the change in temperature has a less marked effect on the rate of physical processes than on the biological reactions. According to this hypothesis, it is suggested that the recovery from non depolarizing drugs is likely to involve a biochemical mechanism.

In a study, where the central body temperature is allowed to decrease gradually from 36.5ºC to 34ºC, the twitch response decreased 20%/ ºC reduction in muscle temperature during a constant infusion rate of vecuronium (Figure 3). The plasma concentrations of vecuronium increased gradually with time suggesting that the pharmacokinetic factors are involved. In control patients where the central body temperature is maintained above 36.5ºC the neuromuscular block and the plasma concentrations of vecuronium remain stable for the duration of a 3 hours infusion. A decrease in body temperature from 36.5ºC to 34.5ºC increased the duration of action of 0.1mg/kg vecuronium from 28 to 62 minutes and the spontaneous recovery time from 37 to 80 minutes respectively. With interest a similar findings have been founded for atracurium and rocuronium. Where the central body temperature is allowed to decrease gradually from 36.5ºC to 34ºC, the twitch response decreased 20% per ºC reduction in muscle temperature during a constant infusion rate of neuromuscular blocking drugs.

In the clinical situation, patients seldom are hypothermic at the induction of anesthesia, more commonly, their temperature decreases over time. The observation that recovery from vecuronium is slow during hypothermia suggests that in the clinical setting where mild hypothermia has developed during the course of anesthesia, the anesthesiologist should anticipate that the duration of action of the supplemental doses of vecuronium may prolonged, and may be this applicable upon most other non depolarizing agents.

Generally speaking, the increased duration of action of muscle relaxants at hypothermia may be caused by changes in pharmacokinetics, pharmacodynamics or both. Hypothermia may influence the action of muscle relaxants by changing the distribution and/or the rate of metabolism and excretion of the drug. Reduced rate of elimination of the drug will result in a slower decline of plasma concentration with time and consequently an increased amount of drug delivered to the neuromuscular junction. Clearance of vecuronium.

Electrolyte imbalance

Potassium ion: Plasma concentration of potassium ion may have a significant influence on the for instance, decreased 10-20%/ºC reduction in central body temperature, which may partly explain the increased duration of action observed in hypothermic patients. It is noticed that the Clearance of 3-desacetylvecuronium did not change with temperature. A similar relationship between central body temperature and plasma clearance occurs with many other non depolarizing neuromuscular blocking agents.

It is suggested that a reduced safety margin exists at the neuromuscular junction with hypothermia, which should have become apparent during partial paralysis in the temperature range of 34-37.5ºC. Therefore, the effect of temperature reduced on the muscle twitch response observed in the absence of muscle relaxants may be related to changes occurring in the contractile apparatus of the muscle rather than at the neuromuscular junction. Experimental studies suggest that hypothermia reduces the sensitivity of the myofilaments to Ca2+ which may explain the altered contractility of cooled muscles.

Neuromuscular transmission, and consequently on the action of muscle relaxants. In the resting state the potassium ion gradient across the endplate is the most important factor act to keeping the resting membrane.

Potential in state of around –90mv. The Nernst equation reveals:

Em(mv)= 61log oK+/iK+

Em = the potential difference across the cell membrane.

oK+ = potassium ion concentration outside membrane.

iK+ = potassium ion concentration inside membrane.

An acute decrease in extracellular potassium concentration if unaccompanied by a similar change in intracellular potassium will hyperpolarizes the membrane, making it more resistant to depolarization by acetylcholine and thus more sensitive to the effect of the non

depolarizing muscle relaxants. Animal studies have demonstrated an increased sensitivity to tubocurarine and pancuronium in chronically potassium depleted animals, and it was found that, there is a decreased sensitivity to the same drugs in conditions when can acute increase in extracellular potassium ion concentration is occurred. The evidences indicate that patients with very low plasma potassium concentration (<2.5mmol/l) whether acute or chronic, will require decreased doses of non depolarizing muscle relaxant.

Calcium ion: The skeletal muscle contraction is relatively independent of extracellular calcium concentration, but it is highly dependent on the intracellular calcium ion concentration. So the anesthetists have no great concern about calcium ion level when the non depolarizing muscle relaxants are used.

Magnesium ion: In skeletal muscles innervations, magnesium ion is an essential regulator of calcium release at the nerve ending and if its concentration increased can compete with calcium ions for the calcium channels. Within skeletal muscles themselves magnesium ion is necessary for normal energy and metabolism, and if it is reduced muscle weakness will occurs. Although magnesium ions are a major regulator of calcium release from the small reserve of the muscle cell but it does not readily penetrate the intracellular space and for this reason magnesium ion is of limited value in the management of malignant hyperthermia.

Magnesium ion however, produces a dose-dependent presynaptic inhibition of neurotransmitter release in peripheral nerves due to competition with calcium for membrane channels on the presynaptic terminal. At the neuromuscular junction magnesium ion concentration of about 5mmol/l and above produce a significant neuromuscular blockade, which is characterized by being reversed by increasing stimulus frequently, and it does not appear to demonstrate fade. Magnesium ion therefore potentiated the action and prolongs the duration of even the shorter-acting non depolarizing muscle relaxant (Figure 4) and may lead to sever muscular weakness in patients with the Lambert-Eaton syndrome or myasthenia gravis.

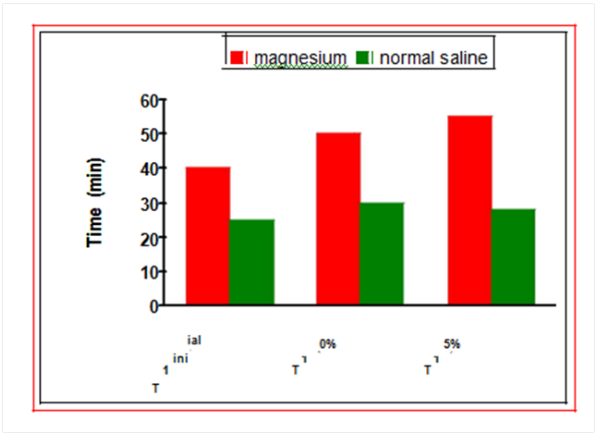

Figure 4 Magnesium ion is potentiated the action and prolongs the duration of even the shorter-acting nondepolarizing neuromuscular blocking drugs.

Non depolarizing relaxants therefore must be used in reduced doses and at increased incremental doses intervals in patients who are significantly hypermagnesmic. Therefore sometimes in some cases a difficulties in reversal of neuromuscular blockade if occurs, calcium may be of use in re-establishing normal motor function. It is of importance to notice that the magnesium ion does not act to shorten the onset time of non depolarizing relaxants. It is generally assumed that magnesium ion may prolong the action of depolarizing relaxants, but this is of no any clinical significance. Acute hypermagnesmic does not affect the duration of a single dose of suxamethonium either in normal subjects or in magnesium-treated pre-eclamptic pregnant mothers. Patients treated with magnesium sulphate do not demonstrate fasciculation and acute administration of magnesium sulphate prior to the use of suxamethonium appear to prevent the release of potassium ion provoked by the relaxant. The possibility exist that magnesium may reduce the incidence and severity of suxamethonium induced muscle pain and may make suxamethonium useable in those circumstances in which the risk of excessive potassium ion release currently make the relaxant contraindicated.

Acid-base changes

Although changes in hydrogen ion concentration (pH) have little effects on neuromuscular transmission itself, acid-base disturbances may influence the effect of neuromuscular blocking agents in many ways. Changes in pH may influence the:

i. Membrane conduction.

ii. Muscle contractility.

iii. Ratio of intracellular to extracellular potassium ion.

iv. Binding properties of the acetylcholine receptors.

v. Affinity of the neuromuscular blocking drugs for the receptor.

It is noticed that the monoquaternary neuromuscular blocking agents (tubocurarine and vecuronium) reacted to acid-base changes differently from the bisquaternary agents (metocurine, pancuronium, and alcoronium). A decrease in pH (acidosis) potentiated tubocurarine and vecuronium block, whereas it antagonize metocurine, pancuronium, and alcoronium block. Reversibly an increase in pH (alkalosis) antagonize tubocurarine and vecuronium block, but potentiated metocurine, pancuronium, and alcoronium block. This opposite effects of the two types of agents was explained on the basis of an alteration in the binding properties of the receptor sites. For the monoquaternary drugs a greater affinity and specificity for the receptors during acidosis is explained by changes in the ionization of the molecules. It is noticed generally that the effects of tubocurarine and vecuronium are especially influenced by acid-base changes, whereas the other non-depolarizing drugs are less influenced.

The antagonism of both pancuronium and tubocurarine by anticholinesterase has been shown to be impaired by respiratory acidosis and metabolic alkalosis. This effect might be the result of depressed muscle contractility, rather than a failure of neuromuscular transmission. However acidosis by itself is known to decrease muscle contractility (twitch tension), whereas alkalosis has the opposite effect. Regarding the depolarizing neuromuscular blocking agent suxamethonium, its effect is antagonized by metabolic and respiratory acidosis.

Drugs interaction at neuromuscular junction

Drug interactions at the neuromuscular junction may take place at, at least three different sites:

I. At the nerve terminal.

II. At the synaptic cleft.

III. At the postsynaptic membrane.

IV. At all the three sites in same time.

Some drugs such as the local anesthetics may interfere with the propagation of the nerve terminal action potential. Others may modify calcium flow into the nerve terminal either by interacting with the calcium channels (aminoglycosides) or by interfering with one or more of the enzymes involved in the control of calcium flow into the nerve terminal (thiophyline and azathioprine) and thus affecting the release of transmitter (Figure 5). Certain drugs (some antibiotics and lithium) are acting by inhibition of the synthesis of acetylcholine.

In the synaptic cleft any drug with anticholinesterase like activity may interfere with the enzymatic hydrolysis of acetylcholine. At post-synaptic membrane some drugs (certain antibiotics) have an effect similar to the nondepolarizing neuromuscular blocking drugs (competitive inhibition), others exert their effects by reducing open-channel life-time, thereby impairing ion channel conductance. Other drugs again may enter and occlude open-ion-channels or promote desensitization process.

Drugs causing increased sensitivity to neuromuscular blocking drugs [promote (augment) relaxation]

Antibiotics: Some antibiotics can produce neuromuscular blockade by their own, although this is seldom seen in usual recommended doses in patients without neuromuscular diseases. However the use (during anesthesia) of certain antibiotics (i.e. aminoglycosides, polypeptides, tetracycline, clindamycin, and lincocin) may increase the sensitivity to neuromuscular blocking drugs and a probability of postoperative recurarization. However, it is found that the neuromuscular block produced by atracurium is not significantly influenced by the presence of therapeutic serum levels of tobramycin or gentamycin, while with vecuronium it is found that the duration of action and time to recovery is significantly increased. The mechanism of action of these antibiotics on neuromuscular blocking drugs is complex and not fully understood. However, suggested mechanisms may include:

a. A reduction in the evoked release of acetylcholine.

b. A decrease in sensitivity of the nicotinic receptors.

c. A channel blockade.

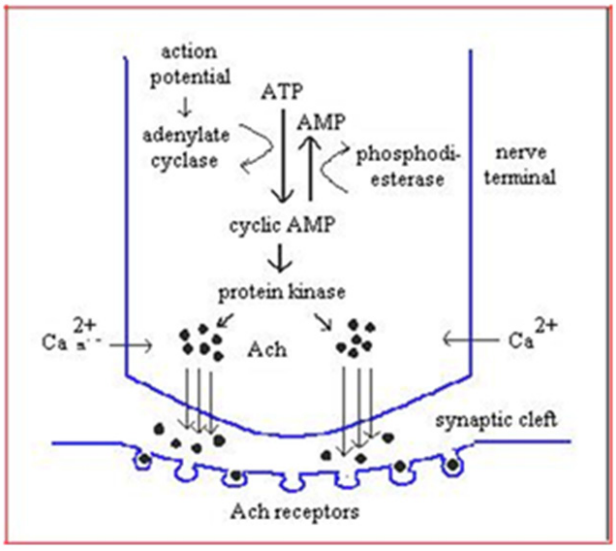

Figure 5 Some drugs may modify calcium flow into the nerve terminal either by interacting with the calcium channels itself [example: aminoglycosides] or by interfering with one or more of the enzymes involved in the control of calcium flow into the nerve terminal [example: thiophyline and azathioprine] and thus affecting the release of transmitter.

However, the channel block may explain why it is difficult to reverse a neuromuscular blockade when polymyxin, clindamycin, or lincocin has been used. However, it is worth noting that channel block is not a competitive in its nature. As channel block is depends on opening of channels, so the greater the activation of the channels the deeper will be the block. Therefore anticholinesterase and calcium may at least theoretically increase channel block by their increasing the activation of receptors.

Inhalational anesthetic agents: They depress neuromuscular function in a dose-dependent way. The inhalational anesthetic agents decrease the release of acetylcholine presynaptically, but the main effect seems to be exerted on the ion channels of the post-synaptic membrane. However volatile anesthetic agents do not bind to the receptor at the acetylcholine binding sites, rather they seem to dissolve in the lipid of the membrane thereby influencing the channel function. They may also bind to the receptor proteins at sites different from the acetylcholine binding sites. Inhalational anaesthetics induce a reduction in junctional conductance by decreasing the gap junction channel opening times and increasing gap junctional channel closing times. They also activates calcium dependent ATPase in the sarcoplasmic reticulum by increasing the fluidity of the lipid membrane. Also appears to bind the D subunit of ATP synthase.

It is postulated also that volatile anesthetic agents increasing blood flow (due to vasodilatation effect), and therefore increasing the relaxant molecules available to muscle. In agreement with this the inhalational anesthetic will potentiated the muscle relaxants, the longer acting nondepolarizing agents such as pancuronium and tubocurarine being more affected than the shorter acting drugs such as atracurium and vecuronium. Enflurane and isoflurane are more powerful than halothane in potentiation of neuromuscular blocking agents. When using potent inhalational anesthetic agents generally the maintenance dose of the neuromuscular blocking drugs may be reduced 25-30%. It is found that anesthetic concentrations of desflurane at equilibrium (administered for 15minutes) reduce the ED95 of neuromuscular blocking drugs (Table 1), (Figure 6) and (Box below).

Table 1 Desflurane in different concentrations [administered for about 15 minutes] reduces the ED95 of neuromuscular blocking drugs

Desflurane concentration	Mean ED_{95} (μg/kg)	
	Pancuronium	Atracurium
0.65 MAC + N_2O/O_2	26	123
1.25 MAC + N_2O/O_2	18	90
1.25 MAC + O_2	22	120

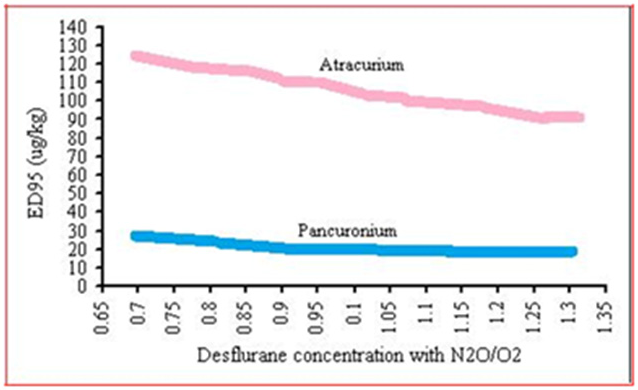

Figure 6 Desflurane in different concentrations [administered for about 15minutes] reduces the ED95 of neuromuscular blocking drugs.

Dosage reduction of neuromuscular blocking agents during induction of anesthesia with desflurane [dosage of neuromuscular blockades may reduced to get rid of potentiation] may results in delayed onset of action suitable for endotracheal intubation or inadequate muscle relaxation. In general the dose of neuromuscular blockade for intubation **should not be reduced**, but the maintenance doses need to be so.

IV anesthetic agents: These drugs may increases the acetylcholine release presynaptically and at the same time decrease the sensitivity of the post-synaptic membrane to acetylcholine, therefore these two effects usually balance out each other. Therefore clinically significant interaction are not seen with the commonly used IV anesthetic agents. Ketamine, however, has been found to potentiate the effect of d-tubocurarine but not others.

Beta-adrenergic blocking agents: It is reported that they have been aggravate or unmask myasthenia gravis and to induce myasthenia syndrome. The most commonly used beta-blocker intraoperatively is the esmolol to reduce tachycardia and hypertension. It is found that esmolol has a minimal partial agonistic activity or direct membrane depressant activity which may be responsible for prolongation of action of nondepolarizing muscle relaxants. In addition catecholamine released intraoperatively causes potentiation of effect of nondepolarizing muscle relaxant by membrane stabilizing effects. It is important to notice that though changes in twitch height is statistically not significant but duration of interaction is significant in respect to elimination half-life, so during use of esmolol one should be conscious about prolonged effect of nondepolarizing muscle relaxants.

Anticholinesterases: Only a relatively small fraction of an administered dose of suxamethonium or mivacurium actually reaches the neuromuscular junction, because the drugs are rapidly hydrolyzed in plasma by plasma cholinesterase during circulation. Drugs that inhibit plasma cholinesterase may therefore make the concentration of these two drugs very high and therefore causes a prolonged response. However in patients with genotypically normal plasma cholinesterase, a decrease in enzyme activity does not cause a very prolonged response (Figure 7). Organophosphate pesticides, cyclophosphamide, ecothiopate eye drops, and bambuterol (carbamylated terbutaline used in the treatment of bronchial asthma) are the drugs most likely to cause clinically significant depression of plasma cholinesterase activity.

Calcium channel blocking drugs: These drugs (verapamil, nifidipine, diltiazem, ----- etc.) do not block neuromuscular transmission itself when used in clinically relevant doses. However it is well established that they potentiated the effect of non depolarizing neuromuscular blocking drugs and that they occasionally may cause difficulty in reversing neuromuscular block with neostigmine. Probably, this effect is relatively unimportant except in situations in which the margin of safety of the neuromuscular junction is reduced. The site of action of the calcium channel blockers is both pre-and post-junctional, but the different drugs may act at different sites. For instance verapamil blocks both the fast sodium channels and the slow calcium channels, while nifidipine blocks the slow calcium channels only.

Local anesthetic drugs: Local anesthetics are fast sodium channel blockers, thus depressing the propagation of nerve impulses, the release of acetylcholine, the sensitivity of the postsynaptic membrane to acetylcholine and the excitability of the muscle cells membrane. So they enhancing neuromuscular block produced by depolarizing and non depolarizing neuromuscular blockades. It has been shown that even normal doses of epidurally injected local anesthetics may potentiate the effect of normal doses of non depolarizing neuromuscular blocking drugs.

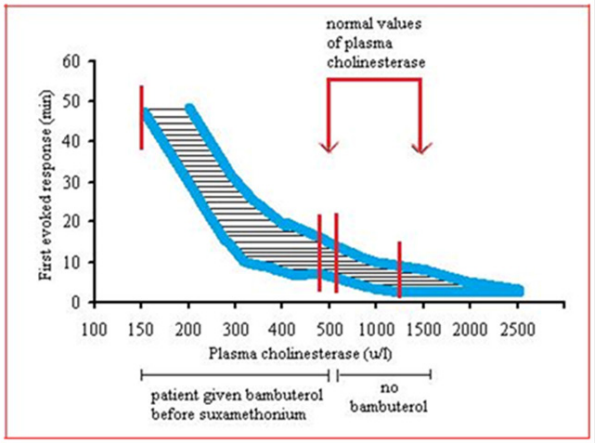

Figure 7 Relation between enzyme activity and time to first evoked response to TOF nerve stimulation following administration of suxamethonium 1mg/kg IV in patients with normal plasma cholinesterase genotype. Line [150 – 500] represent a patient given bambuterol 130mg orally 2 hours before the suxamethonium administration, line [500 – 1500] represent patients not given bambuterol. Mean curve and 95% prediction interval is indicated.

Magnesium sulphate: May decrease acetylcholine release from the nerve terminal, reduces the sensitivity of the post-junctional membrane to acetylcholine, and depresses the excitability of the muscle cell membrane. Accordingly magnesium has been shown to enhance neuromuscular block for all neuromuscular blocking drugs. Several cases have been reported of prolonged neuromuscular block in patients with preeclampsia and preeclamptic toxemia treated with magnesium sulphate. However calcium can antagonize the effect of magnesium sulphate.

Other drugs: For instance the long term use of steroids may results in a myopathy. The effect of myopathy is mentioned later in [chapter - clinical]. The enhanced neuromuscular blockade produced when corticosteroids are combined with (for example) vecuronium may augment pharmacological denervation and contribute to the pathophysiology of prolonged weakness observed in some critically patients. Dantrolene depresses skeletal muscle directly and impairs excitation-contraction coupling.

Relaxant combination: Relaxants when given in combination and their effect will be either additive or synergistic. The additive effect is usually due to purely post-synaptic effect, while synergistic effect is may due to differential actions on pre- and post-synaptic sites.

Drugs causing decreased sensitivity to neuromuscular blocking drugs [resist relaxation]

Some antiepileptic drugs (phenytoin and carbamazepine), azothioprine (used as an immunosuppressant agent for organ transplantation), some corticosteroids, and methyl xanthenes (aminophyline and thiophyline) have been reported to cause resistance to the effect of nondepolarizing neuromuscular blocking drugs. Aminophylline and azathioprine are phosphodiesterase inhibitors. An inhibition of phosphodiesterase in the nerve terminal would result in an increased level of cyclic adenosine monophosphate (cAMP) and possibly also of acetylcholine. However in general the mechanisms underlying these effects are uncertain.

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Conflicts of interest

The author declare there is no conflicts of interest.

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