SUMMARY: Neuromuscular blocking agents (NMBAs) have been widely used to control patients who need to be immobilized for some kind of medical intervention, such as an invasive procedure or synchronism with mechanical ventilation. The purpose of this monograph is to review the pharmacology of the NMBAs, to compare the main differences between the neuromuscular junction in neonates, infants, toddlers and adults, and moreover to discuss their indications in critically ill pediatric patients. Continuous improvement of knowledge about NMBAs pharmacology, adverse effects, and the many other remaining unanswered questions about neuromuscular junction and neuromuscular blockade in children is essential for the correct use of these drugs. Therefore, the indication of these agents in pediatrics is determined with extreme judiciousness. Computerized (Medline 1990-2000) and active search of articles were the mechanisms used in this review.


Since the introduction of the neuromuscular blocking agents (NMBAs) in 1942, a marked evolution has occurred in these drugs, with progressive increase in their potency combined with fewer risks or adverse effects. Many of these NMBAs have appeared in the last 10 years, with an increase in their use in intensive care units. On the other hand, the development of new drugs has made the choice of agents much more complex, due to differences in pharmacology, clinical indications, and side effects of each new drug. The NMBAs have been routinely given to critically ill patients to facilitate tracheal intubation, for muscle relaxation during surgery (generally abdominal and thorax surgery) and to patients who offer resistance to mechanical ventilation (despite the use of intense analgesia and sedation).

In this review, we analyze the pharmacology of and indications for the old NMBAs, and we also review the clinical and pharmacologic advances of the new agents as well as their complications.

Physiology of neuromuscular transmission and blockade

Definition: The neuromuscular blockade can be defined as a reversible interruption of neuromuscular transmission in the Acetylcholine (AcC) nicotinic receptors, fin the absence of any analgesic, sedative or amnesic action. In summary, the normal neuromuscular transmission is related to the stimulation of the postsynaptic junctional receptors of AcC that aroused the depolarization and muscular contraction. Nicotinic Receptors: The neuromuscular junction contains some types of nicotinic receptors:
- Two on the muscle surface;
- one junctional;
- one extrajunctional;
- one presynaptic receptor on the parasympathetic-nerve ending.

The postsynaptic receptors are proteins with five subunits: α, β, χ, δ e ϵ. Each neuromuscular junction contains 1–10 million nicotinic receptors.

Physiology of neuromuscular transmission: The neuromuscular transmission initiates when a nerve impulse arrives on the presynaptic nerve endings, with liberation of AcC molecules. The AcC- liberated molecule crosses the junctional cleft to stimulate the postsynaptic receptors.

To begin the opening of the channel receptors, which allow the movement of ions that will finally depolarize the end plate, 2 AcC molecules must bind simultaneously to two a sub-
units of a postsynaptic receptor. When this happens, a brief opening (1 msec.) of the channel occurs, with a non-selective passage of sodium and calcium to the muscle, leading to depolarization of the muscular membrane and muscular contraction.

Then the AcC molecule is quickly broken down by the enzyme acetylcholinesterase in the junctional cleft, stopping the muscular contraction.

Physiology of the neuromuscular blockade: The neuromuscular blockade can exist by two distinct mechanisms:

• **Depolarizing neuromuscular blockade;**
  The neuromuscular blockade by the classic pathway (depolarizing), begins when a drug bind to the a subunit of the nicotinic receptors like the molecule of AcC does. In the beginning, an initial opening of the ion channel produces a contraction (fasciculation). After this, the depolarization of muscular membrane is sustained (persistent depolarization), since the drug is not broken by acetylcholinesterase, leading to neuromuscular block.

• **Nondepolarizing neuromuscular blockade;**
  In the nondepolarizing neuromuscular blockade, the drugs bind in a competitive way (with AcC) to at least one a subunit of the nicotinic receptors. Since there is no binding of at least two molecules of AcC, there is no opening of the ion channels and no muscular depolarization, with the muscle becoming flacid.

### Classification of NMBAs

The NMBAs are classified as follows:
1) Based on the pharmacologic mechanism:
   a. Depolarizing drugs;
   b. Nondepolarizing drugs.
2) Based on the biochemical structure:
   a. Benzylisoquinolinium derivatives;
   b. Aminosteroids compounds.
3) Based on the duration of the desired effect:
   a. Short-acting drugs;
   b. Intermediate-acting drugs;
   c. Long-acting drugs.

The NMB drugs have many indications and adverse effects. For this reason, anaesthesiologists and intensivists are trying to systematize the choice of the “ideal N MBA”, which has to: have rapid onset of action and ease of reversion; have low toxic levels; have few autonomic and cardiovascular effects; are metabolized and excreted independently of the final organic function; and have low cost.

### Depolarizing agents (agonists)

**Succinylcholine (Sch):** Succinylcholine is considered a nondepolarizing junction (NMJ) is still developing. In this maturation phase, the receptors have an increased metabolic activity.

The main point that distinguishes the immature receptors from the developed ones is a functional difference that occurs due to a prolonged opening of the ionic channels. This allows the immature muscles to be more easily depolarized, and these receptors have also a greater affinity for depolarizing agents and lower affinity for nondepolarizing agents.

One of the age-related particularities is the alteration in the degree of neuromuscular blockade with the body composition and the drug distribution. Since the NMBAs distribute in the extracellular fluid exclusively, and since neonates and infants have a larger extracellular compartment with a higher volume of distribution, neonates and infants require high doses of NMBAs to reach the desired effect. This difference is decreased in toddlers and school-aged children that have a volume of distribution close to Adults.

Concerning the alterations concerning the type of muscular fibers (type I, or slow-twitch, and type II, or fast-twitch), it is important to note that the type I fibers are more sensitive to NMBAs as compared to type II fibers. Type I fibers have clinical relevance, since the diaphragm of a neonate has fewer type I fibers as compared to a diaphragm of a toddler or an adult. This makes the diaphragm of an infant more reactive to NMBAs than his own peripheric musculature.

### Particularities of neuromuscular blockade in children

There are some characteristic points in the neuromuscular junction that differentiate newborns and infants from other ages.

In the first 2 months of life (in particular the newborn), the neuromuscular junction (NMJ) is still developing. In this maturation phase, the receptors have an increased metabolic activity.

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### Depolarizing agents (agonists)

**Succinylcholine (Sch):** Succinylcholine is considered a nondepolarizing...
larizing NMBA with short action and is the only nondepolarizing agent available for clinical use today. Due to its fast initial action, the main indication of this drug is for tracheal intubation (considered the first choice in recent review)\textsuperscript{10}. Succinylcholine (Sch) is formed by 2 joined AcC molecules and rapidly hydrolyzes into succinic acid and choline by the (pseudo) cholinesterase in patients with normal levels of this enzyme.

Succinylcholine acts by stimulation of the cholinergic receptors (activation of the NM junction) that leads to depolarization of the musculature. This causes primarily a muscular contraction or fasciculation.

Succinylcholine has an onset of action of 30 to 60 seconds and a duration of 3 to 5 minutes (I.V.). The typical blockade of Sch (or phase I blockade) is obtained in normal doses of 1 to 2 mg/kg/dose. In cumulative doses higher than 2 to 4 mg/kg, a alteration in the type of blockade is obtained (competitive blockade or phase II blockade) with a nondepolarizing action. This drug has hepatic metabolism, and 10% of the drug is excreted unchanged in urine.

Some clinical situations can change the levels of the plasma cholinesterase, which can lead to prolonged neuromuscular blockade (Table 1).

The most important side effects and complications of Sch use are:
1) Complications related to depolarization (muscular fasciculation and pain, increase in the intracranial pressure, increase in the intragastric and intraocular pressure and displacement of compound fracture);
2) Prolonged neuromuscular blockade (plasma cholinesterase deficiency);
3) Cardiovascular effects (dysrhythmias – generally bradyarrhythmias in children, with recommendation to dispose of atropine for immediate use);
4) Anaphylaxis;
5) Myoglobinemia and myoglobinuria;
6) Hyperkalemia;
7) Malignant hyperthermia (associated with inhalation anesthetics)\textsuperscript{13, 14, 15}.

### Nondepolarizing agents (antagonists)

**Short action**

**Mivacurium:** Until the appearance of rapacuronium, mivacurium was the only nondepolarizing NMBA classified as a short-action drug. It is derivative from benzylisoquinolinium, with 3 times the potency of atracurium (which is a secondary derivative)\textsuperscript{14}.

It has an onset of action of 1 to 3 minutes and duration less than 30 minutes. This drug is metabolized by plasma cholinesterase (and is altered in the same clinical situations mentioned in Sch). It is excreted in the urine. The normal dose is 0.2 mg/kg/dose.

The potential side effects are:
1) Prolonged neuromuscular blockade in cases of plasma cholinesterase deficiency or renal failure (metabolites with renal excretion);
2) Histamine release in rapid infusions (but with hypotension rarely observed)\textsuperscript{3, 6, 15}.

**Rapacuronium:** Rapacuronium is the newest non-depolarizing NMBA. This drug is not yet approved for clinical use by the FDA and is under clinical investigation in children. In adults, rapacuronium has shown an onset of action as rapid as succinylcholine, with decreased duration as compared to mivacurium. Recent studies show a similar effect in children, with little cardiovascular effects and histamine release\textsuperscript{16}.

**Intermediate action**

**Atracurium:** Atracurium is a bisquaternary intermediate NMBA (an ammonium benzylisoquinolinium). It has an onset of action of 2 minutes with a peak in 5 to 10 minutes. Its duration is about 40 to 60 minutes. Atracurium is metabolized by spontaneous degradation (Hoffman elimination), a non-enzymatic separation that occurs at normal temperature and pH. Atracurium is degraded into acrylate and laudanosine, which are initiators of neuromuscular blockade. Laudanosine has been associated with central nervous system stimulation and convulsion.

The normal dose is 0.4 to 0.8 mg/kg/dose (initial) and 2 to 15 mcg/kg/minute (continuous infusion).

Hypotension and histamine release can be associated with rapid infusion of the drug. Cutaneous erythema is a common manifestation. Another disadvantage of atracurium is the necessity of higher doses in cases of prolonged use. Its main advantage is the difference in its metabolism and the possibility of use in patients with renal or hepatic failure\textsuperscript{3, 6, 14, 17}.

**Cisatracurium:** Cisatracurium is a cis-cis isomer of atracurium. It is a drug with the same characteristics of atracurium but stimulates less histamine release and less laudanosine production. It has 4 times the potency combined with low cost as compared with its isomer. Despite its advantages, there are a few studies about the use of this drug in adults and even fewer studies in children\textsuperscript{3, 6, 14}.

**Vecuronium:** Vecuronium is a aminosteroid derivative of

### Table 1 – Clinical situations of diminished plasma cholinesterase.

<table>
<thead>
<tr>
<th>Hepatic disease</th>
<th>Organophosphate</th>
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<tbody>
<tr>
<td>Infants until 2 months of life</td>
<td>Cyclophosphamide</td>
</tr>
<tr>
<td>Burns</td>
<td>Neostigmine</td>
</tr>
<tr>
<td>Extra-corporeal circulation</td>
<td>Malnutrition</td>
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<tr>
<td>Uremia</td>
<td>Plasmapheresis</td>
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pancuronium, with an alteration in its structure (molecular position of 2 methyl N-piperidine). This structural alteration considerably reduces the vagolytic effects (tachycardia and hypertension) observed with pancuronium. It has an onset of action of 1 to 3 minutes and duration of 30 to 40 minutes (dose dependent). Vercuronium is metabolized 40% to 50% in the liver, and after hepatic hydrolysis, 3 of its metabolites have neuromuscular blocking activity (one of them with 70% of the action). These metabolites are excreted in the urine (with 15% of accumulation in patients with renal failure). Its main disadvantage is the prolonged neuromuscular blockade. About 30% to 40% of this drug is metabolized by the liver, and it is excreted in the urine (with up to 40% unaltered drug, which could lead to prolonged neuromuscular blockade). The recommended dose is 0.04 to 0.1 mg/kg.

**Pancuronium:** Since its introduction in 1967, pancuronium has been the most used NMBA by anesthesiologists and intensivists. It is a synthetic aminosteroid that has an onset of action of 2 to 3 minutes and half-life of 110 minutes.

**Rocuronium:** Rocuronium is an aminosteroid derivative of vecuronium with intermediate-to-short action. It was recently approved for clinical use by the FDA (1990). It has the same characteristics of vecuronium with higher potency (10% to 15%). This drug has minimal cardiovascular effects (just a little increase in cardiac output, and after hepatic hydrolysis, 3 of its metabolites have neuromuscular blocking activity (one of them with 70% of the action). These metabolites are excreted in the urine (with 15% of accumulation in patients with renal failure). Its main disadvantage is the prolonged neuromuscular blockade.

**Doxacurium:** Among the benzylisoquinolinium derivatives, doxacurium is the most recently approved for clinical use. It is the most potent NMBA (10 times more potent than d-tubocurarine) with slow action. It has an onset of action of 6 to 11 minutes and a duration of 60 minutes. This drug binds with plasma proteins (30%) with minimum metabolism and is eliminated unaltered in the urine and bile.

The dose is 0.03 to 0.05 mg/kg/dose.

**Indications and drug selection**

The main indications for the use of NMBAs are based on the optimization of immobility of the patient for procedures like:

- **Short-term (less than 6 hours):**
  1. tracheal intubation;
  2. high-risk invasive procedures.
- **Long term (more than 6 hours):**
  1. synchrony with mechanical ventilation (dysynchrony, excessive hyperventilation or hyperventilation, nonconventional ventilation);
  2. reduction of metabolic demand or work of breathing;
  3. treatment of intense agitation unresponsive to higher doses of analgesia and sedation;
  4. therapeutic hypothermia (decreased shivering);
  5. protection of surgical repairs.

It’s important to remember that in all these indications, the use of NMBAs should be considered in patients that deep sedation and analgesia have failed to reach the desired effect.

The choice of the best NMBA becomes very difficult and dependent on the degree and necessity of the muscular relaxation desired. So the basic criteria should be followed when one is making the choice for the more adequate NMBA: patient’s age, onset of action and duration of the drug (depending on the final goal), presence or absence of hemodynamic instability, association with other drugs, presence of organ failure (renal or hepatic); potential risks and side effects (in short and long term), presence of previous disease, and the drug’s cost. Pharmacologic data about the main NMBAs are on Table 2.

In September of 1995, the Society of Critical Care Medicine published an official statement and best practice parameters for the use of NMBAs. The 2 recommendations concerning the use of NMBAs were classified as level 2 or reasonably justifiable by available scientific evidence and strongly supported by expert critical care opinion. The first recommendation was to use pancuronium as the preferred NMBA for most critically ill patients, justified by the few adverse cardiovascular consequences and the low cost – an alert was given for the use in patients with renal or hepatic failure (to use lower doses). The second recommendation was to use vecuronium as the first option in patients with cardiac disease or hemodynamic instability, with lower doses in patients with renal or hepatic failure.

It is important to note that this con-
sensus was made for adult patients, and it must be carefully interpreted for pediatrics since the cardiac effects of pancuronium are very expressive in children.

**Monitoring the neuromuscular blockade**

Despite its difficulty in daily practice, the monitoring of the neuromuscular blockade should be used routinely in intensive care units, due to the wide variations in the degree of blockade between the patients. It is very hard to identify the response exactly in terms of the beginning, the degree, and the duration of the neuromuscular blockade. Therefore, monitoring becomes important for documenting the presence and degree of blockade and the return of the normal neuromuscular transmission.

Monitoring of the effects of these drugs is done by the the stimulation of the ulnar nerve and observation of the evoked response in the adductor muscle by a force transductor, by electroneuromyography, or by visual inspection.

There are 3 patterns of nerve stimulation: 1) simple stimulus (0.1 to 0.15 Hz); 2) train-of-four (2 Hz per 4 seconds or 4 impulses of 0.5 second, repeated every 10 seconds), and 3) tetanic stimulus (50 to 100 Hz per 5 seconds) 3,25.

**Complications of the use of NMBAs**

The great majority of complications after the use of NMBAs are associated with long term utilization.

In the last decade, the major described complication is the prolonged muscle weakness after its discontinuation. This complication is well documented in children, generally with the use longer than 48 hours. This effect could last for up to 6 months 24. There are 2 patterns of neuromuscular dysfunction: the persistent block of the NM junction (PBNMJ) and the acute myopathy 25.

PBNMJ is the complication that has more clinical significance, probably due to the accumulation of drugs or its active metabolites (mainly in patients with renal or hepatic failure). Another pattern of PBNMJ is the one that begins when an aminosteroid NMBA and corticosteroids are used together 26,27. This association of drugs is important since one of the major indications of NMBAs in pediatrics is the child with status asthmaticus with dyssynchrony with mechanical ventilation (and who uses short or long-term corticosteroids). This kind of PBNMJ was also recently described with the association of benzylisoquinolinium derivatives and corticosteroids 28.

The acute myopathy also leads to prolonged paralysis, but is not caused by delayed recuperation of the NM junction 25.

Muscular atrophy, joint contractures, thrombotic or embolic events, ulcers of the skin, atelectasis, pneumonia, and corneal drying are other possible complications. Special attention should be given to the neurologic evaluation of the patient receiving NMBAs (attention to status epilepticus and monitoring with electroencephalogram) and the assessment of pain and anxiety (sweaty brow, tearing, hypertension, and tachycardia could be signs of pain or anxiety) 3,5,6,9.

With the knowledge of all these complications, the NMBAs should be used only when profound analgesia and sedation have failed to reach the desired effect and when used, bolus doses are preferred and continuous and prolonged infusions should be avoided.

**Final considerations**

The NMBA continue to be frequently used drugs in pediatric intensive care units. Continuous updating concerning the pharmacology of the NMBAs (mainly the new ones) is necessary for the correct evaluation of the indications for each drug and to avoid adverse effects. Many questions about the physiology of the neuromuscular junction and about the NMBAs and their complications in children remain unanswered, which indicates a very judicious use of these drugs in children.
RESUMO


Os bloqueadores neuromusculares têm sido amplamente utilizados para controlar pacientes que necessitam imobilidade para algum tipo de intervenção médica, desde a realização de procedimentos invasivos até a obtenção de sincronismo com a ventilação mecânica. O objetivo básico desta monografia é revisar a farmacologia dos principais bloqueadores neuromusculares, analisar as diferenças existentes na junção neuromuscular de neonatos, lactentes, pré-escolares e adultos, além de discutir suas indicações em pacientes criticamente enfermos internados em unidade de terapia intensiva pediátrica. Revisão computadorizada da literatura (Medline 1990-2000) associado a busca ativa de artigos comusearam o mecanismo de busca dos dados desta revisão.


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