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Neuromuscular Blocking Agents in Critically Ill Children

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Abstract

Neuromuscular blockade is used in critically ill children for a variety of reasons. The physiology and pharmacology of neuromuscular blocking agents is reviewed. The effect of hypothermia on the pharmacodynamics of neuromuscular blockade is discussed. The ideal agent would have a rapid rate of onset with spontaneous reversal after discontinuation. Patients receiving neuromuscular blocking agents need to be assessed for the degree of blockade that is being sustained. The need to temporarily discontinue infusions of neuromuscular blocking agents to enable an assessment of the level of sedation or to allow an assessment of neuromuscular function is highlighted.

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Indications for neuromuscular blockade

There are many recognised indications for starting treatment with neuromuscular blocking agents in critically ill children. These may include facilitation of endotracheal intubation and prevention of patient-ventilator dyssynchrony during mechanical ventilation. This may be particularly important during "unphysiological" mechanical ventilation such as deliberate hypo- or hyperventilation, inverse ratio ventilation and high frequency oscillatory ventilation.

Certain medical conditions may require the institution of neuromuscular blockade such as in the treatment of tetanus, malignant hyperthermia or neuroleptic malignant syndrome. In some circumstances neuromuscular blockade may be instituted to reduce oxygen consumption by reducing the work of breathing and metabolic demand, and may facilitate treatment of head-injured patients and those undergoing induced hypothermia in order to prevent shivering. Occasionally, specific surgical repairs may need to be protected in the post-operative period such as tracheal reconstructions, cricoid split procedures and vascular anastamoses.

In some circumstances neuromuscular blockade is undertaken purely to prevent the patient from moving in order to facilitate an invasive procedure or to prevent inadvertent self-extubation where agitation is unresponsive to maximal sedation and analgesia. It must be remembered that neuromuscular blocking agents provide no analgesia and possess no amnesic qualities, and that neuromuscular blockade is no alternative to satisfactory sedation and analgesia.

Despite the examples of indications for neuromuscular blockade listed above, it should be remembered that little objective data exists to

demonstrate a clear benefit in using these drugs in the critically ill on the intensive care unit. Indeed in the setting of head injury there is contradictory evidence as to the safety of routinely using neuromuscular blocking agents to control intracranial pressure. There are suggestions from Hsiang and colleagues that this practice may be detrimental to long-term outcomes[1].

Historical aspects of neuromuscular blockade

The Italian monk Peter Martyr d'Anghera first described the poisoned arrows used by South American Indians in 1516[2]. Sir Walter Raleigh provided further reports following his visit to Guinea in the last years of the 16th century[3]. Many of these early reports of the deaths of individuals affected by the arrow poison recount a convulsive rather than a paralytic death and it has been suggested that this may have been due to the contamination of the poison with strychnine from the roots and bark of the plant *Strychnos toxifera*.

The German chemist Boehm classified curares according to their means of preparation[4] and Benjamin Brodie provided the first scientific assessments of such arrow poisons in experiments on donkeys and chickens[5]. Brodie demonstrated that curare killed its victims by stopping their breathing and went on to demonstrate how an ass who had been paralysed with curare could be kept alive by artificial ventilation, using bellows inserted into the trachea. Finally, Claude Bernard elucidated the action of curare on the neuromuscular junction in experiments published between 1857 and 1866[6]. In the 1920s and 1930s the precise actions of curare were clarified and in 1942 Harold Griffith and Enid Johnson[7] described the use of a curare preparation during surgical anaesthesia.

Physiology of the neuromuscular junction

Nerves extend from the brainstem (in the case of cranial nerves) or the spinal cord to muscle cells. Signals are transmitted along axons, which are insulated by myelin, at conduction speeds of up to 50–100 m/s. In most mammalian muscles each muscle fibre has a single region of contact with the axon of the motor neurone that supplies it where transmission is chemical rather than electrical as is the case in the axon. This specialist structure is the neuromuscular junction; the gross morphology of which was demonstrated by Kühne over 100 years ago. In the 1930s workers at University College, London demonstrated that the acetylcholine released at the motor nerve endings served to amplify and modulate the effect of motor nerve activity on muscle[8]. The role of the neuromuscular junction is to facilitate transmission of the electrical impulse from the nerve terminal to the motor end plate on the muscle. This is achieved by the transmission of acetylcholine across the 60–100 nanometre synaptic cleft. Acetylcholine is incorporated into 60 nanometre vesicles, each containing about 10,000 molecules of acetylcholine, found mostly near the synaptic membrane, and bound by a lipid membrane bilayer. Electrical transmission occurs when acetylcholine arrives at and causes the depolarisation of the motor end plate.

An action potential originating from the central nervous system is propagated to the nerve terminal; this causes an influx of calcium that in turn initiates the exocytotic release of acetylcholine-containing vesicles into the synaptic cleft. The acetylcholine liberated by this process rapidly diffuses across the synaptic cleft and binds to acetylcholine receptors on the motor end plate of the muscle fibre. The end plate is oval in shape, and about 20–30 µm across, and extensively folded. Receptor density is very high at the endplate with 10–20 000 receptors μm^{-2}, or 10^{6-7} per end plate. These acetylcholine receptors are pentameric ring-like structures 6.5 nanometres in diameter with a central pore of 2.5 nanometres. Each receptor projects into the extracellular space for 5.5–6.5 nanometres and extends for 1.5–2.0 nanometres into the cytoplasm of the muscle. In the resting state the receptor is twisted so that the central pore is closed. The pentamer has a life cycle of 4–6 days with receptors constantly being replaced in healthy innervated muscle.

Binding of two acetylcholine molecules to the α units of the acetylcholine receptor produces a conformational change in the receptor that results in the opening of the central pore, which stays open for between 1 and 10 ms. This in turn results in the influx of some 10^5 sodium ions, which increases the membrane potential from –90 millivolts to approximately 0 millivolts. At this point potassium channels open to allow the efflux of potassium ions. When the end plate potential at the motor end plate reaches a threshold value of around –50 millivolts voltage-dependent sodium ion channels of the adjacent muscle membrane open and the initiation of an action potential occurs. This is propagated throughout the muscle fibre and results in muscle contraction. The effects of acetylcholine are terminated by its dissociation from the acetylcholine receptor and its subsequent degradation via acetylcholinesterase into acetate and choline. These breakdown products are then

reabsorbed into the nerve terminal and are reconstituted into acetylcholine.

Physiologically, the requirement for repeated stimulation suggests there is a large excess of acetylcholine stored in the nerve terminal, sufficient for perhaps 10^4 stimulations. There is good evidence for the existence of nicotinic receptors on the presynaptic membrane, but rather than providing positive feedback and increasing the amount of acetylcholine available for release, it is likely that these function by mobilising stores and increasing synthesis. Thus acetylcholine increases its own synthesis and mobilisation.

Acetylcholine release is further modified by presynaptic and adrenoceptors. Receptors for dopamine, GABA, opioids, substance P, serotonin, prostaglandins, glutamate and angiotensin II have also been described.

Hypothermia

Hypothermia has been used in critically ill children to minimise neurological injury and following cardiac surgery. In their experiments on rat phrenic nerve preparation in 1951, Holmes and colleagues first suggested that cold antagonised the neuromuscular blockade produced by curare[9]. Similar findings in humans were produced by Canard, Zaimis and colleagues; who concluded that cold potentiates depolarising neuromuscular blockade and antagonised non-depolarising neuromuscular blockade[10,11]. In the early 1970s induced hypothermia was a common technique during cardiac surgery.

It soon became clinically apparent that the requirements for non-depolarising neuromuscular blocking agents were reduced at lower temperatures. In 1973 Feldman demonstrated an approximately 50% fall in the adductor pollicis twitch response to ulnar nerve stimulation following a fall in forearm muscle temperature of 4–5 -C[12]. At around this time further rat phrenic nerve data from Foldes and colleagues contradicted the earlier reports of Holmes[13]. Similar evidence of the potentiation of neuromuscular blockade by non-depolarising drugs was produced by other investigators in cats[14]. It is now believed that the original experiments of Holmes and Zaimis were flawed by technical factors.

This effect has primarily been studied in adult patients undergoing hypothermic coronary artery bypass grafting[15,16], neurosurgery[17], during post-operative recovery[18] or in fit adults under experimental conditions[19].

It is recommended by the manufacturer that atracurium be stored at temperatures between 2 and 8 ^{o}C, although only minimal loss of activity has been demonstrated with storage at room temperature for up to 3 months[20]. Variations of temperature within the physiological range are not felt to significantly alter the offset time of atracurium. However, the use of therapeutic hypothermia has been shown to produce a significant prolongation of the offset time of atracurium when administered by continuous infusion in critically ill children[21]. During induced hypothermia it has been demonstrated that the dose requirement of atracurium to maintain a constant level of neuromuscular blockade in adults is reduced by 43% during cardiopulmonary bypass at 26 ^{o}C[22], and by 35% at 30 ^{o}C[23].

Cold may affect neuromuscular conduction and the action of muscle relaxants in several ways (Table 1).

It has been known since the observations of Lorenté de No that cold reduced neural conduction. Experimental findings by many investigators including Hodgkin and Katz, and Halar and colleagues have confirmed these findings[24]. It is most likely that the effect of cold

Table 1. Possible effects of hypothermia on neuromuscular condition and the action of muscle relaxants

Motor nerve conduction
Synthesis, storage or mobilisation of acetylcholine
Acetylcholine release and synaptic transmission
Action of acetylcholinesterase
Muscle contraction
Cell membrane repolarisation
Pharmacokinetics of neuromuscular blocking agents, by interfering with metabolism, renal or hepatic excretion

on nerve conduction is mediated by the action of hypothermia on the potassium channels at the node of Ranvier.

Diminished output of acetylcholine results in reduced competition for receptors and therefore allows greater duration of action of non-depolarising neuromuscular blocking agents. Many aspects of the process of synthesis, storage and mobilisation of acetylcholine require a transfer of energy. This usually occurs through the calmodulin-adenosine triphosphatase mechanism, the action of which would be expected to be reduced at low temperatures. The active carrier mechanism by which choline is transported into the motor nerve is affected by cold. The further acetylation of choline is an active enzymatic process that can be depressed *in vitro* by low temperatures. Processing acetylcholine into vesicles and their subsequent mobilisation are energy-dependent and therefore temperature-sensitive. These effects are small in comparison to the normally excessive amounts of acetylcholine released but are likely to become clinically significant in the presence of non-depolarising neuromuscular blocking agents.

Katz and Miledi have demonstrated increased synaptic delay during hypothermia[25]. The release of acetylcholine from vesicles requires calcium activation of synaptotagmin and synaptophysin. This mechanism may be reduced by cold, as may the process of acetylcholine receptor activation following diffusion across the synaptic cleft. The physical transmission of acetylcholine across the cleft is much less likely to be affected by cold.

Repolarisation of cell membranes involves the sodium/potassium pump mechanism that is energy-dependent and therefore temperature-sensitive. Delayed repolarisation would be expected to increase muscle contractility and potentiate the action of depolarising neuromuscular blocking agents. Delayed repolarisation of the nerve spike potential and decreased muscle tension are both felt to contribute to the effects seen during hypothermia.

Atracurium is broken down primarily by two purely chemical mechanisms; Hofman degradation (a non-enzymatic base-catalysed reaction first described at the turn of the century) and non-specific ester hydrolysis via plasma cholinesterase. One possible mechanism by which cold may affect the metabolism of atracurium is by retarding the process of Hofman degradation. This seems less likely in the face of evidence that hypothermia has a similar effect on the duration of action of vecuronium[22], which is not thought to undergo Hofman degradation. More recent evidence suggests that changes at the neuromuscular junction and in the contractile apparatus of the muscle cell have a more significant effect, impaired release of acetylcholine and a reduced rate of generation of muscle contraction[12,26–30]. Given the effects of temperature on the neuromuscular junction and muscle function there are necessary questions regarding the validity of neuromuscular monitoring techniques in these circumstances. It is known that hypothermia affects train-of-four (TOF) stimulation[31] and it may be that we are not just measuring a prolongation in the duration of action of atracurium but also a decline in the effectiveness of the neuromuscular complex. Heier[32] has demonstrated a reduction in twitch tension during hypothermia between 35 and 34 °C, but no effect on the TOF ratio. Eriksson[33], however, has demonstrated a linear relationship between skin temperature and TOF ratios, showing that whilst above 32 °C TOF ratios show only a minimal reduction, they are significantly reduced at skin temperatures below 32 °C.

Interestingly, animal experiments have demonstrated that the nearer the animal species studied is to a hibernating or poikilothermic genus, the less likely is cold to depress neuromuscular conduction. In humans and higher animals cold depresses neuromuscular conduction to a greater extent than its effect on muscle contraction.

Monitoring of neuromuscular blockade

In most intensive care units the degree of neuromuscular blockade is monitored clinically by watching carefully for spontaneous voluntary movement and respiratory effort. This subjective assessment is important but is made more difficult by several factors which include the sporadic nature of spontaneous movements and the significant differences that can exist in the degree of neuromuscular blockade between the diaphragm and the peripheral muscles. Also, whilst clinical monitoring may be able to identify the patient who is receiving insufficient neuromuscular blockade, it cannot identify those receiving excessive doses of these agents which may be an important clinical situation.

The transcutaneous stimulation of the ulnar nerve is the most common method of monitoring the degree of neuromuscular blockade. In this way the response of the adductor pollicis muscle can be observed by visual, tactile or electro-mechanical means. Several different patterns of electrical stimulation are available for the stimulation of peripheral nerves; of these the

train-of-four (TOF) pattern is used most frequently. This method of stimulation is less painful, more reliable and more easily interpreted at the bedside than other methods. During TOF stimulation four supramaximal stimuli are delivered at 2 Hz and this can be repeated at short intervals. In the absence of neuromuscular blockade, TOF stimulation results in the generation of four equal twitches of the adductor pollicis and the thumb. The ratio of the amplitude of the fourth twitch (T_4) to the first twitch (T_1) in the same train provides a convenient method for the assessment of the degree of neuromuscular block. As the proportion of neuromuscular junctions blocked increases the T_4 of the TOF decreases in amplitude when compared to the T_1. As the blockade becomes deeper the third twitch (T_3) the second twitch (T_2) and finally the T_1 are depressed until the T_4 is lost entirely. This occurs at approximately 75% depression of T_1. Both T_4 and T_3 responses are lost at approximately 80% depression of T_1 and T_4, T_3 and T_2 are suppressed at around 90% depression of T_1.

Peripheral nerve stimulation can be difficult to perform and errors can arise because of technique, the device or the patient. Peripheral oedema, haemodynamic status and hydration frequently vary during an intensive care admission and can produce variation in TOF response. In small children it is easy to produce direct stimulation of muscle groups which will prevent accurate monitoring of the neuromuscular junction. The results of tactile or visual evaluation of TOF responses are variable[34] and even accurately collected TOF data can be of limited value. It is well known that TOF data obtained by stimulation of the ulnar nerve does not accurately reflect the neuromuscular state of the diaphragm; recovery of the diaphragm usually precedes that of the adductor pollicis. There are also many examples where TOF monitoring does not correlate well with the clinical state of the patient; some individuals may be capable of considerable movement in the presence of a TOF response that would otherwise indicate a satisfactory level of neuromuscular blockade[35]. Many factors can influence the depth of neuromuscular blockade beside neuromuscular blocking agents; acid-base derangement and electrolyte disturbances can all potentiate neuromuscular blockade, whilst different drugs have been shown to either potentiate or antagonise blockade[36].

Despite the limitations which apply to the use of peripheral nerve stimulation it has become a popular technique on critical care units to assess the degree of neuromuscular blockade. The main reasons for this are the ease with which the technique can be instituted and interpreted. More recently the use of TOF monitoring in attempts to optimise the degree of neuromuscular blockade has been shown to reduce the total dose requirements of patients for neuromuscular blocking agents and allow faster recovery of neuromuscular function and spontaneous ventilation[37], and allows cost savings[38].

Complications of neuromuscular blockade

The adverse effects of neuromuscular blocking agents can be divided into the pharmacological effects of the drugs themselves and the effects of the physical immobility that they produce.

Several of the neuromuscular blocking agents available can produce ganglion and vagal blockade and result in liberation of significant amounts of histamine. Together these can produce adverse cardiovascular effects such as hypotension, tachycardia or bradycardia.

Prolonged immobility can result in muscle atrophy and joint contractures, pressure sores, pulmonary atelectasis and associated pneumonia, and corneal drying with the potential for permanent corneal damage. These problems can all be anticipated and should be effectively prevented, minimised and treated where necessary.

A further consequence of immobility is the restriction it places on the effective neurological assessment of the patient. If used during status epilepticus, neuromuscular blocking agents can completely obscure many of the clinical manifestations of seizure activity. In the absence of electroencephalography this may result in an unnecessary delay in effective seizure treatment. Medical and nursing staff should be aware that the accurate assessment of the level of sedation in patients receiving neuromuscular blocking agents can be difficult. Responses such as changes in heart rate and blood pressure, sweating and lacrimation are variable and their absence cannot be interpreted as ensuring patient comfort. The descriptions of those individuals able to recall the experience of neuromuscular blockade with inadequate sedation are frightening and should encourage us to alter our practice to minimise this possibility. In the future, it is possible that analysis of the electroencephalogram (EEG) may be useful in assessing the degree of sedation in children receiving neuromuscular blocking agents. Neurophysiology offers a potential non-invasive, objective, and continuous measurement of brain function.

Much work needs to be done before EEG monitoring of sedation can be routinely performed

on the intensive care unit. The newer algorithms such as the EEG bispectral index seem the most promising and also include features of signal quality estimation and artefact rejection that make them better suited to the intensive care environment where electrical interference can make EEG recording difficult.

One of the most widely reported complications associated with the administration of neuromuscular blocking agents is that of prolonged muscle weakness or frank paralysis [39]. In the early 1990s several case reports were published describing critically ill patients who were left paralysed for unexpectedly prolonged periods following the discontinuation of a continuous infusion of a neuromuscular blocking agent. This problem can prolong the period of mechanical ventilation, increase the risk of complications, prolong hospital admission and produce a need for expensive rehabilitation services. In initial cases the prolonged paralysis appeared to be due to the accumulation of the active 3-desacetyl metabolite of vecuronium in patients with renal failure. This problem has also been evident following the concomitant administration of aminosteroid neuromuscular blocking agents and corticosteroids and aminoglycosides. Subsequently reports emerged of similar problems associated with the administration of benzylisoquinolinium compounds such as atracurium.

Confounding the diagnosis of prolonged neuromuscular blockade due to muscle relaxants is the recognition of a critical illness polyneuropathy syndrome. Such patients may develop weakness and impaired deep tendon reflexes after sepsis and multiple organ dysfunction. Witt and colleagues have demonstrated axonal degeneration of motor and sensory nerve fibres in 70% of patients with sepsis and multiple organ failure[40]. Many of the adult patients so described had not received neuromuscular blocking agents and the spectrum of these two problems has not been clearly defined.

Several monitoring and dosing techniques have been suggested to decrease the incidence of prolonged weakness after neuromuscular blockade. Most importantly, as with any treatment, the use of neuromuscular blocking agents should be restricted to situations where the benefits clearly outweigh the possible risks. Several authors have suggested that the use of peripheral nerve stimulation can be of benefit in reducing the dose of neuromuscular blocking agents administered; although it has not been demonstrated that such a measure can reduce the incidence of prolonged weakness. Data suggesting a defect in neuromuscular transmission after prolonged block has lead to the suggestion that intermittent discontinuation may be helpful. This approach also allows for an accurate assessment of the level of sedation and for thorough neurological examination of the patient. Intermittent dosing has also been suggested as a further way of reducing prolonged weakness but this technique may be hampered by the increased risk of histamine release and subsequent hypotension with agents such as atracurium.

Features of the ideal muscle relaxant

Ideally muscle relaxation would be achieved by depressing the most sensitive part of the transmission process, which is the neuromuscular conduction between nerve and muscle. Interference with the process of acetylcholine formation, storage, mobilisation, release, or by antagonising its effects at acetylcholine receptors would seem to be the ideal method. Drugs such as hemicholinum or vesamicol depress acetylcholine production but produce a very gradual impairment in neuromuscular transmission that is of no clinical use in the critical care setting[41]. Similar drawbacks apply to drugs such as botulinum toxin, which interfere with acetylcholine storage and mobilisation. Drugs that act at pre-synaptic receptors, such as pentamethonium, all possess ganglion–blocking properties that make them unsuitable for use as neuromuscular blocking agents. Currently drugs that act at the post-synaptic receptor sites, such as α-bungarotoxin, are also too slow in onset of action and too long lasting to be of use in the intensive care unit.

All neuromuscular blocking agents probably act at both pre-synaptic receptors and at post-synaptic receptors to a varying degree[42]. Synergism of these effects means that the ideal neuromuscular blocking agent would have such a dual action and result in a faster rate of onset of blockade and a reduced dose requirement to produce the necessary clinical effect.

The ideal neuromuscular blocking agent would have a rapid rate of onset and would reverse spontaneously, quickly after discontinuation. The ideal duration of action of such drugs is a matter of debate. Some would argue for a range of drugs with varying durations of action. In critical care practice a short-acting agent that could be continuously infused is probably the most useful profile. Many of the neuromuscular blocking agents in common use already have the benefit of minimal cardiovascular side effects, and their

metabolites do not tend to affect the function of the central nervous system, liver or kidneys.

Ideally neuromuscular blocking agents should not be associated with the release of histamine. In practice this effect does not frequently cause clinical problems and it should be noted that there is little relationship between drugs that cause histamine release and the occurrence of anaphylactoid reactions. A typical example of this is suxamethonium, which does not release histamine but which is associated with the highest incidence of serious anaphylactoid reactions of all the neuromuscular blocking agents.

Commonly used neuromuscular blocking agents

The neuromuscular blocking agents may be described by their mechanism of action as either depolarising or non-depolarising. Features of the commonly used agents are shown in Table 2. Drug interactions affecting neuromuscular blocking agents are shown in Table 3.

Suxamethonium

Suxamethonium is the only commonly used depolarising drug producing rapid, profound and short-lived muscle relaxation, dissociating from the acetylcholine receptor about 1000 times more slowly than acetylcholine. In the critical care setting the use of suxamethonium is restricted to emergency endotracheal intubation because of the many complications associated with its use. Infants and children require more suxamethonium per kilogram than adults to achieve the same degree of neuromuscular block. In order to facilitate endotracheal intubation a dose of 3mg/kg is recommended for neonates and infants, 2 mg/kg for children and 1 mg/kg for adults. Onset of neuromuscular blockade is typically within 60 seconds and usually lasts for between 5 and 10 minutes. In the absence of intravenous access intramuscular administration at a dose of 4 mg/kg has been described in children[43]. When given by this route one can expect maximum onset of blockade within 3 to 5 minutes and a duration of action of between 19 and 23 minutes.

Many of the unwanted effects of suxamethonium are related to the structrual similarity between suxamethonium and acetylcholine. Suxamethonium can occupy not only the acetylcholine present at the neuromuscular junction but also those in the central nervous system, autonomic ganglia, cardiac tissue, smooth muscle, adrenal medulla and secretory glands. Bradycardias, tachycardias and arrhythmias may be seen in clinical practice particularly after the use of large or repeated doses of intravenous suxamethonium. In addition the depolarisation which occurs before the onset of neuromuscular block can produce muscle pain and increases in intracranial and intraocular pressure. Muscle fasciculation occurs in 40–75% of cases, more commonly in women and less commonly in children. Myalgia occurs in 40–50% of cases and myoglobinaemia and myoglobinuria can result in renal dysfunction.

Hyperkalaemia is an important clinical problem associated with suxamethonium. In normal individuals an increase in serum potassium of approximately 0.5 mmol/l is seen following suxamethonium administration. This may become a significant clinical problem in certain clinical circumstances where there is a large population of immature extra-synaptic acetylcholine receptors. Denervation of mammalian muscle produces an abnormal distribution of nicotinic receptors with an increase in fetal subtypes initially distributed in clusters at extrajunctional regions near the endplates. These then spread in a random manner over the whole membrane of the denervated muscle. Turnover of these extrajunctional receptors occurs within two days and is much more rapid than that of junctional receptors. They also have an increased sensitivity

Table 2. Features of commonly used neuromuscular blocking agents when used in children

	Initial dose (mg/kg)	Infusion dose (mcg/kg/min)	Onset time (minutes)	Clinical duration (minutes)
Suxamethonium	2	–	0.6	5.8
Pancuronium	0.15	0.5–1.0	2–4	24
Vecuronium	0.15	1.5–2.5	1–3	22
Rocuronium	0.8	5–10	0.8–1.5	27
Atracurium	0.5	10–20	1–3	25
Mivacurium	0.2	16	1–2	11

Table 3. Drug interactions affecting neuromuscular blocking agents (NMBs)	
Drugs potentiating the of NMBs	**Drugs antagonising the action action of NMBs**
Aminoglycosides β -Adrenergic blockers Calcium channel blockers Ciclosporin Clindamycin Cyclophosphamide Dantrolene Diuretics Lignocaine Lithium carbonate Magnesium Procainamide Quinidine Tetracycline	Carbamazepine Phenytoin Ranitidine Theophylline

to acetylcholine and when stimulated they remain open for approximately ten times longer than junctional receptors at 100 milliseconds. These differences in behaviour are a result of differing substructures; normal adult junctional receptors contain ε subunits that are replaced by γ subunits in the fetal type along muscle fibres. In this setting the administration of suxamethonium can result in sudden large increases in serum potassium that may result in cardiac dysrhythmias and cardiac arrest. Other clinical circumstances resulting in the generation of extrajunctional receptors include immobility, crush injuries, burns, irradiation and the prolonged administration of neuromuscular blocking agents. Following denervation, sensitivity to suxamethonium begins within 3 to 4 days and maximises at around 7 days but persists for several months[44,45].

Other problems associated with suxamethonium include the prolonged neuromuscular blockade that occurs in the presence of plasma cholinesterase deficiency, anaphylaxis and malignant hyperthermia. Malignant hyperthermia is an inherited myopathy characterised by a hypermetabolic state that is triggered when the patient is exposed to anaesthetic agents including suxamethonium and volatile agents. The syndrome is thought to be due to a reduction in the reuptake of calcium by the sarcoplasmic reticulum necessary for termination of muscle contraction. Consequently, muscle contraction is sustained, resulting in signs of hypermetabolism, including acidosis, tachycardia, hypercarbia, glycolysis, hypoxaemia, and hyperthermia. Management of this problem involves the discontinuation of the triggering agent and administration of the agent dantrolene.

Pancuronium

Non-depolarising neuromuscular blocking agents commonly used include the aminosteroid drugs pancuronium, vecuronium and rocuronium. It was the demand for a neuromuscular blocking agent that did not produce hypotension that lead to the development of pancuronium by David Savage at the Organon Laboratories in Scotland. Although widely used, the cardiovascular effects of this drug limit its usefulness; pancuronium causes tachycardia, which in combination with an increased peripheral vascular resistance can cause an increase in the work of the myocardium.

Vecuronium

Vecuronium is a monotertiary, monoquaternary derivative of pancuronium that is slightly more potent than the parent compound and was introduced into anaesthetic practice in 1980. Although it does not produce a rapid onset of action, vecuronium is notable for its marked lack of side effects, even in high doses[46]. The major route of elimination is hepatobiliary, and metabolites have some neuromuscular blocking activity. The renal excretion of these metabolites explains the accumulation that may be seen in adult patients in renal failure. Differences in volume of distribution produce a longer duration of action in younger children.

Rocuronium

Rocuronium is a more recently developed drug which has the benefit of a rapid onset of action, approximately half that of vecuronium. In high doses it does cause some vagolysis but overall it represents best non-depolarising neuromuscular

blocking agent currently available for facilitating endotracheal intubation. It should be remembered however that neuromuscular blocking agents have differential effects on different muscle groups, and the onset of laryngeal adductor paralysis with rocuronium is significantly slower than with suxamethonium.

Atracurium

Atracurium, a bisquaternary tetrahydropapaverum derivative, is one of the benzylisoquinolinium family of drugs and was originally synthesised at the University of Strathclyde following extraction of the substance petaline from the Lebanese plant, *Leontice leontopetalum,* and was patented in 1977[47]. Atracurium is not a pure drug and can form 10 different isomers; in the commercial preparation three isomers predominate: Trans-trans, cis-trans and cis-cis. Atracurium is a particularly useful non-depolarising neuromuscular blocking agent for use in the critically ill[48]. Single doses have a relatively rapid onset of action; endotracheal intubation can usually be achieved within 90 seconds of the intravenous injection of 500-600 microg/kg, with an elimination half-life of 21 minutes.

It is the unique metabolism of atracurium that makes it so useful in the intensive care setting. It is broken down primarily by two purely chemical mechanisms; Hofman degradation and non-specific ester hydrolysis via plasma cholinesterase. The extent to which non-specific ester hydrolysis contributes to the total breakdown of atracurium is debated and in rodents it constitutes the major mode of metabolism. The rate of metabolism is faster for the trans-trans and trans-cis isomers than for the cis-cis isomer; only a small proportion of which is metabolised by the cholinesterase. Some organ uptake has been demonstrated and 10% of the drug is excreted in the urine.

Breakdown of atracurium results in the generation of two inactive derivatives; a tertiary amino by-product, laudanosine, and an inactive monoquaternary residue. Laudanosine produces electroencephalographic changes at concentrations over 2 microg/ml and has been shown capable of producing seizures at concentrations over 17 microg/ml in dogs. Despite the presence of detectable levels of laudanosine however, human subjects have not experienced any central nervous system effects[49]. Without evidence of significant accumulation, the effects of atracurium have not been shown to be prolonged in renal or hepatic failure. Children may require a higher dose of atracurium than adults to maintain neuromuscular blockade owing to the faster rate of clearance of the drug in this age group[50]. Cautious use in neonates is recommended in view of possible toxicity recently described[51].

One clinically significant effect of prolonged infusions of atracurium is that of tolerance. Several authors have described tolerance to atracurium in adults and children[52,53] and there may be cross-resistance to both atracurium and other non-depolarising neuromuscular blocking agents[54]. A number of mechanisms have been proposed to explain this finding, and one of particular importance is the formation of extrajunctional acetylcholine receptors as has been previously discussed[55]. In this setting an increasing proportion of any neuromuscular blocking agent will be bound at an extrajunctional site and will thus be ineffective. Normal muscle activity is an important factor in reducing the number of extrajunctional acetylcholine receptors and animal studies have demonstrated that prolonged immobilisation results in a similar degree of resistance to atracurium as that produced by an infusion of the drug itself. More recently studies have emerged suggesting that prolonged infusions of neuromuscular blocking agents can themselves produce denervation-like changes in skeletal muscle, even without causing immobilisation or paralysis[56]. A further possible mechanism for atracurium resistance is an increase in drug binding to $alpha_1$ acid-glycoprotein; an acute phase protein whose levels increase in a number of conditions including inflammation, trauma, infection and cancer[57].

Mivacurium

Mivacurium is a benzyllisoquinolinium derivative of atracurium which has 3 times the potency of the parent compound and is notable for having the shortest duration of action of any non-depolarising neuromuscular blocking drug available for clinical use. Mivacurium is hydrolysed by plasma cholinesterase at 88% of the rate of suxamethonium, this produces a duration of action approximately twice that of suxamethonium. Like atracurium, mivacurium is available as of a mixture of three stereoisomers.

Neuromuscular blocking practice

Merriman surveyed British practice in 1981 and found that 91% of intensive care units used neuromuscular blocking agents frequently[58]. When Bion later surveyed adult intensive care units in 1987, the frequent use of neuromuscular blocking agents had decreased to 16%[59].

Hansen-Flaschen and colleagues produced their report on the use of sedative and neuromuscular

blocking agents in intensive care in the USA in 1991[60]. They found that 70% of units used these agents occasionally, 26% used them frequently and only 2% used them routinely. Peripheral nerve stimulators were never used in 79% of units, and occasionally used in a further 14%; in only 4% of units were they routinely used. In this study pancuronium was the most commonly used agent, followed by vecuronium and atracurium. Intermittent intravenous injection was the preferred route of administration for neuromuscular blocking agents at that time. The following year, in 1992, Klessig and colleagues found that vecuronium was the most commonly used neuromuscular blocking agent[61] and reported that only 34% of anaesthetic intensivists used peripheral nerve stimulators to monitor neuromuscular blockade.

Matthews surveyed 16 of the existing 22 UK paediatric intensive care units in 1991 with a questionnaire that detailed four clinical cases (epiglottitis, head injury, aspiration pneumonitis and a neonate requiring post-operative ventilation)[62]. Four neuromuscular blocking agents were mentioned; vecuronium was the most commonly suggested agent, followed by atracurium, pancuronium and then curare.

In 1995 a task force of more than 40 experts in disciplines relating to the use of neuromuscular blocking agents in the intensive care unit was convened from the membership of the American College of Critical Care Medicine and the Society of Critical Care Medicine[63]. A consensus was reached after a review of personal experience and of the published literature. Three recommendations were arrived at for achieving sustained neuromuscular block in critically ill patients.

1. Pancuronium is the preferred neuromuscular blocking agent for most critically ill patients.
2. Vecuronium is the preferred neuromuscular blocking agent for those patients with cardiac disease or haemodynamic instability in whom tachycardia may be deleterious.
3. Patients receiving neuromuscular blocking agents should be appropriately assessed for the degree of blockade that is being sustained.

Despite what appears to be a trend towards the less frequent use of neuromuscular blocking agents, one can still find references in the literature to an earlier time where the use of such agents was rare, and recommending a return to the basic principles of human caring[64].

Conclusions

The administration of neuromuscular blocking agents by continuous infusion is commonplace on the paediatric intensive care unit. It may be desirable to temporarily discontinue such infusions to enable an assessment of sedation and to allow an assessment of neuromuscular function. Little is known regarding the pharmacokinetics or pharmacodynamics of such infusions when used in critically ill children and in particular whether tolerance is a practical problem in this group of patients. Reduced doses should be used in children in whom therapeutic hypothermia is used.

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