Review Article

The use of muscle relaxants in the intensive care unit

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Neuromuscular blocking agents are frequently used in the Intensive Care Unit to facilitate tracheal intubation and the application of continuous paralysis. This review will focus on various conditions of the critically ill patient such as multi-organ dysfunction, acid-base and electrolyte imbalance, prolonged immobility, multiple drug interactions and specific disease/injury processes that may affect the pharmacokinetic and pharmacodynamic behaviour of muscle relaxants. As such, due to the complex nature of the critically ill patient, the effects of neuromuscular blocking agents are unpredictable. Therefore, guidelines regarding their administration and the methodology and requirement for continuous bedside monitoring of neuromuscular function will be presented.

En réanimation, on utilise souvent les myorelaxants pour faciliter l'intubation endotrachéale et maintenir un niveau de paralysie constant. Ce travail passe en revue les conditions propres au grand malade comme les défaillances polyviscérales, les dérangements acido-basiques et électrolytiques, l'immobilisation de longue durée, les interactions médicamenteuses et les effets de différentes pathologies en cause sur le comportement pharmacocynétique et pharmacodynamique des myorelaxants. Ainsi par la complexité des difficultés rencontrées, leurs effets chez le malade dont l'état est critique sont difficiles à prédire. Une ligne de conduite gouvernant leur administration et le monitorage continu qu'elle nécessite sont présentés.

Key Words

NEUROMUSCULAR RELAXANTS: succinylcholine, atracurium, vecuronium, pancuronium, mivacurium, pipecuronium, doxacurium;
INTENSIVE CARE: paralysis;
MONITORING: neuromuscular function.

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There are a variety of conditions in the Intensive Care Unit (ICU) whereby the application of a continuous neuromuscular block may improve patient management (Table I). Despite this, few studies have examined the use of muscle relaxants in this patient population. As such, no guidelines exist and the methodology of administering neuromuscular blocking agents to the ICU patient varies from clinician to clinician and is based on clinical experience. Concern regarding the serious consequences that may occur during continuous paralysis has also had an impact upon their use (Table II). In addition, case reports have recently implicated muscle relaxants in causing generalized weakness, following their long-term administration which required recovery periods from two days to six months.[1-7] However, it is not clear whether muscle relaxants were a precipitating factor since other possible contributing conditions were present, e.g., polyneuropathy of critical illness,[8] disuse atrophy,[9] aminoglycoside, and steroid administration.[5,6,10,11] This potential problem warrants further investigation.

Drug selection

There are many characteristics of a muscle relaxant to be considered before its administration (Table III). The critically ill patient who may benefit from long-term muscle paralysis often presents with underlying multi-organ dysfunction and depends upon inotropic support for haemodynamic stability. Therefore, the choice of relaxant is individualized to each patient and primarily dependent on (i) the pathophysiology of the disease process, (ii) the potential side effects of the muscle relaxant and its propensity to cause haemodynamic instability and (iii) whether the patient is capable of metabolizing/excreting the drug appropriately.

TABLE I Indications for continuous muscle paralysis in the critically ill patient

Decreased pulmonary/chest wall compliance with coexisting high ventilatory pressures, e.g., ARDS.
Patient/ventilator non-compliance.
Raised intracranial pressure.
Central neurogenic hyperventilation.
Tetanus.
Status epilepticus.
To reduce metabolic demands/work of breathing.
To prevent shivering during therapeutic cooling.

TABLE II Potential complications of muscle paralysis in the critically ill patient

Unrecognized patient-ventilator disconnection.
Suppression of cough reflex.
Secretion retention and atelectasis.
Pulmonary infection.
Patient immobility causing
– deep vein thrombosis and pulmonary emboli
– peripheral nerve injuries
– skin breakdown/stasis ulcers.
Inability to spontaneously perform a neurological examination.
Inadequate sedation in the paralyzed patient.
Subluxation of unstable spinal fractures.
Side effects of the muscle relaxant.

TABLE III Characteristics to consider when choosing a neuromuscular blocking agent

Speed of onset.
Potential for cardiovascular stability.
Dependency on renal/hepatic function for metabolism.
Potential for histamine release.
Potential for "cumulative" effect.
Ease and rapidity of antagonism.
Predictable action.
Intermittent or continuous infusion administration capability.
Potential for induction or inhibition of hepatic enzymes.
Potential formation of toxic or active metabolites.
Interactions with other drugs.
Cost.

This review will discuss the pharmacokinetic and pharmacodynamic properties of the muscle relaxants currently available. Particular emphasis will be placed on how multi-organ dysfunction may influence the choice of muscle relaxant used and its effects on drug doseages. Bedside monitoring of neuromuscular block will also be discussed.

Depolarizing muscle relaxants

Succinylcholine

Succinylcholine (1.0–1.5 mg · kg^{-1}) offers a profound and the most rapid onset of neuromuscular block (60–90 sec).[12] Therefore, it is the relaxant of choice during clinical situations where an expedient tracheal intubation is desirable. For example, the uncooperative hypoxic patient who requires tracheal intubation and institution of positive pressure ventilation.

METABOLISM

Succinylcholine is rapidly hydrolyzed by plasma cholinesterase and its duration of action is six to eight minutes after a dose of 1 mg · kg^{-1}.[12] Duration of action can be prolonged due to (i) a decrease in effective plasma cholinesterase (e.g., homozygous atypical plasma cholinesterase (incidence approximately 1/3200),[13] pregnancy,[14] and liver disease),[15] (ii) a reduction in activity due to the administration of anticholinesterases,[16] e.g., echothiopate iodide, neostigmine, pyridostigmine, edrophonium or (iii) drugs known to antagonize plasma cholinesterase (e.g., cyclophosphamide, monoamine oxidase inhibitors, oral contraceptives, insecticide poisoning).[13] With the exception of atypical plasma cholinesterase, the duration of action in these situations may be prolonged by approximately 20 min which should not cause any clinical complications.[17] With atypical plasma cholinesterase, the duration of block may be hours and if unrecognized, may be interpreted as an acute "neurological event" leading to inappropriate and expensive tests, e.g., CAT scan of the head. Furthermore, patients who require frequent clinical monitoring of neurological function, e.g., after acute head injury, a prolonged partial neuromuscular block may impede proper neurological assessment. Therefore, if it is necessary to antagonize this block, administration of fresh frozen plasma is effective. Plasma stored for seven weeks at −70° C has no loss of plasma cholinesterase activity.[18]

Continuous infusion

The use of succinylcholine for long-term muscle paralysis is impractical. For procedures of short duration under general anaesthesia (10–15 min), a 90% block can be maintained with an infusion rate of 60 μg · kg^{-1} · min^{-1}; however, considerable variation exists between patients (range 20–110 μg · kg^{-1} · min^{-1}).[19,20] In our ICU experience, a rate of administration of 50 μg · kg^{-1} · min^{-1} provides adequate relaxation for short procedures such as bronchoscopy and recovery occurs within 10–15 min after termination of infusion. Longer periods of infusion or higher doses are associated with tachyphylaxis and phase II block; the latter may be antagonized within 15 min with neostigmine (0.036 mg · kg^{-1}) or edrophonium (0.1–0.2 mg · kg^{-1}).[21,22] It is recommended that a peripheral nerve stimulator be used in order to titrate the infusion.

SIDE EFFECTS

Despite the potential side effects of succinylcholine (Table IV) it is frequently used for tracheal intubation. With the

TABLE IV Complications associated with succinylcholine

Hyperkalaemia.	
Muscle pain/fasiculations.	
Myoglobinaemia/myoglobinuria → renal dysfunction.	
Increase serum CPK.	
Bradyarrhythmias.	
Increased intraocular pressure	during
Increased intragastric pressure	depolarizing
Increased intracranial pressure	phase of block
Malignant hyperthermia.	
Prolonged blockade.	
Anaphylaxis.	

TABLE V Contraindications to succinylcholine

Absolute
Suspected "difficult airway."
Hyperkalaemia.
Suspected malignant hyperthermia or myotonia.
Tetanus.

Relative
Sepsis.
Massive trauma.
Burns.
Spinal cord transection.
CNS injuries/infections.
Prolonged immobilization.
Disuse atrophy.
Abnormal plasma cholinesterase.
Decreased plasma cholinesterase activity.
Open-eye injury.
Guillain-Barré syndrome.
Peripheral nerve injury.

exception of the patient in whom difficult tracheal intubation is anticipated, the contraindications to succinylcholine (Table V) are primarily attributed to conditions in which its administration may cause hyperkalaemia.[23] Normally there is an increase of serum potassium of approximately 0.5 $mEq \cdot L^{-1}$ due to leakage of potassium from the muscle cell during depolarization.[24] High serum potassium concentrations have been reported after succinylcholine in patients with cord transection or nerve damage, burns, major trauma, CNS injuries and prolonged periods of immobility.[25] Recommendations for the safe use of succinylcholine in these situations are based on case reports and therefore vary from one injury process to another.

Denervation and burn injuries

Hypersensitivity to succinylcholine occurs following a denervation or burn injury due to muscle endplate receptor multiplication. This phenomenon takes days to develop but a hyperkalaemic response usually is evident by three to five days. Succinylcholine is therefore safe to use in the early injury period (<24 hr).[9] Maximal sensitivity occurs by seven to eight days.[26,27] Therefore, succinylcholine is contraindicated in acute hemiplegia[28] or paraplegia[29] during the period at least seven days[30] after injury until six months.[31] In burn patients, Schaner *et al.* defined the period of vulnerability between 20 and 60 days which was extended if burn wound infection occurred.[32] The severity of hyperkalaemia is related to the burn area and the dose of succinylcholine and increases have been sufficient to cause cardiac arrest.[33] Furthermore, prior administration of a defasiculating dose of a non-depolarizing muscle relaxant does not guarantee ablation of this response.[25]

Trauma

Hyperkalaemia has been documented in major trauma patients who had received succinylcholine and is postulated to result from a pathophysiological process initiated by direct muscle trauma. The period of susceptibility is defined from one week to 60 days post-trauma or until adequate healing has occurred and the degree of hyperkalaemia is related to the severity of injury.[34]

CNS injuries

There are two case reports of hyperkalaemia occurring in closed head injury patients (without paresis), who received succinylcholine during a general anaesthetic 31 and 60 days after trauma.[35,36] Hyperkalaemia has also been reported in patients with ruptured cerebral aneurysms who received succinylcholine 10 to 50 days following rupture.[37] It is not clear whether the hyperkalaemic response is due to prolonged immobility, as previously described,[25] or is associated with the underlying injury.

Controversy exists whether succinylcholine should be used in patients who may have increased intracranial pressure (ICP), e.g., as a result of a head injury. Small increases in ICP have been detected in patients with previously normal ICP after administration of succinylcholine.[38,39] Minton *et al.* hypothesized that this was due to increased afferent activity from muscle spindles during fasiculation causing an increase in cortical electrical activity and cerebral blood flow.[38] Therefore, whether this increase in ICP would be exaggerated in patients with increased ICP is unknown. On the other hand, the advantage of succinylcholine in a patient requiring tracheal intubation is that it induces a rapid and profound neuromuscular block which prevents any substantial increase in ICP as a result of coughing during the intubation process.

SPINAL FRACTURES

The use of muscle relaxants for tracheal intubation in patients with cervical spine trauma is controversial. It is argued that the patient who is paralyzed will have considerable spinal movement during oral tracheal intubation and in-line traction which may result in neurological injury

TABLE VI

Drug	*Intubating dose* ($mg \cdot kg^{-1}$)	*Intermittent dose*[a] ($mg \cdot kg^{-1}$ *q1–3hr*)	*Continuous infusion*[a] ($\mu g \cdot kg^{-1} \cdot min^{-1}$)	*Clinical duration*[b] *(min)*	*Duration of action*[c] *(min)*	*Relative cost*[d]
Short-acting						
Succinylcholine	1.0–1.5	-	60	5–10	12	1
Mivacurium	0.15–0.20	-	6–7	17	24	N/A[e]
Intermediate acting						
Atracurium	0.5–0.6	0.6–1.2	5–6	30	64	80:1
Vecuronium	0.1–0.15	0.15–0.3	100–200	30	45	70:1
Long-acting						
Pancuronium	0.1–0.15	0.05–0.1	20–40	60	160	35:1
Pipecuronium	0.07–0.08	N/A	N/A	70	N/A	N/A
Doxacurium	0.05–0.06	0.005–0.01	N/A	83	N/A	N/A

[a]Requires continuous neuromuscular monitoring due to patient variability.
[b]Time from injection to 25% twitch recovery.
[c]Time from injection to 90% twitch recovery.
[d]Relative cost of intubating dose ($2 \times ED_{95}$) compared to succinylcholine.
[e]Data not available.

or worsening of an existing injury.[40,41] There are no reports which support this hypothesis. On the other hand, a retrospective review of 150 patients with traumatic cervical spine injuries showed no difference in neurological outcome whether intubation was performed awake (45% of patients) or following administration of anaesthesia and muscle relaxants (55% of patients). They recommended that airway management should proceed with care and common sense and not be dictated by a dogmatic approach.[42]

In summary, the advantages of succinylcholine for use in the ICU are its rapid onset, ability to produce a profound neuromuscular block, and low cost.

Non-depolarizing muscle relaxants

Atracurium

Intravenous doses of 0.3–0.6 $mg \cdot kg^{-1}$ produce adequate conditions for tracheal intubation within two minutes followed by a rapid rate of recovery (duration of block is from 20–30 min after a dose of 0.5 $mg \cdot kg^{-1}$, Table VI).[43] An incremental bolus technique, often used during general anaesthesia, would require too frequent administration to provide a steady-state neuromuscular block. A continuous infusion (5–9 $\mu g \cdot kg^{-1} \cdot min^{-1}$) is therefore recommended.[44] Recovery following long-term infusions have indicated rapid recovery times.[44–46] In a study of 33 patients who received infusions for a mean duration of 90 hr, the average recovery time was 39 min following its termination.[44] Furthermore, reversal may be hastened to within minutes by administration of an anticholinesterase; the agent of choice is edrophonium due to its more rapid onset of action.[47]

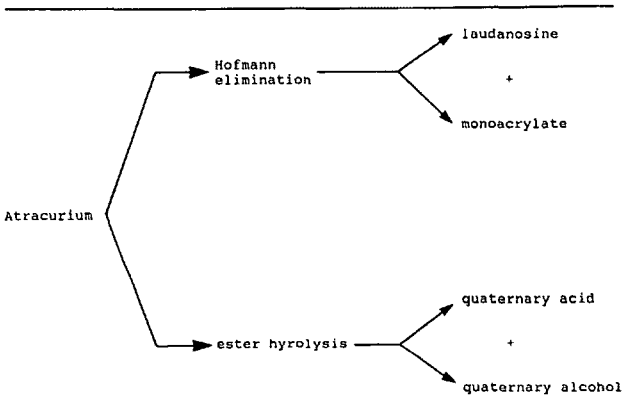

FIGURE Pathways of atracurium metabolism and the metabolic byproducts.

METABOLISM/EXCRETION

Controversy still exists about the precise mechanism of atracurium metabolism. The majority of atracurium is metabolized via Hofmann elimination which is the spontaneous degradation of atracurium at physiological pH and temperature into laudanosine and a monoquaternary acrylate. The remainder undergoes ester hydrolysis by non-specific plasma esterases (Figure).[48,49] Since Hofmann elimination does not require organs/enzymes for its metabolism, there is no significant prolongation of action of atracurium in patients with renal and/or hepatic dysfunction following a single or incremental bolus technique or during continuous infusion.[50–56] Furthermore, there is no evidence of a "cumulative effect," i.e., the duration and magnitude of blockade is greater than predicted following additional drug boluses, in patients with renal failure. The ease of reversibility of neuro-

muscular blockade is similar to patients with no renal dysfunction.[44–46,57,58] These pharmacokinetic characteristics of atracurium are attractive for long-term infusions in critically ill patients whose renal and hepatic function may be precarious as a result of the effects of the underlying illness and/or toxic effects of drugs, e.g., aminoglycoside nephrotoxicity.

The theoretical concerns for long-term infusions of atracurium are its metabolic byproducts laudanosine and monoacrylate (Figure). Laudanosine is a central nervous system stimulant and has caused seizures in dogs following large intravenous boluses (13–22 $mg \cdot kg^{-1}$).[59] Hofmann elimination releases two molecules of laudanosine for each molecule of atracurium. Therefore the amount of laudanosine formed is dependent upon the proportion that undergoes Hofmann elimination.[49] In humans, laudanosine levels (200–300 $ng \cdot ml^{-1}$), have been detected following a single bolus of atracurium (0.5 $mg \cdot kg^{-1}$). However, these concentrations are less than the threshold required to cause seizures in dogs (17 $\mu g \cdot ml^{-1}$).[50,59] The seizure threshold level in humans is not known. Although laudanosine concentrations are increased in renal failure patients, renal elimination accounts for only 4–9% while the remaining portion is dependent upon hepatic metabolism.[50–52,60,61] The highest serum level of laudanosine ever measured in a human was 5.1 $\mu g \cdot ml^{-1}$ following five days of continuous infusion of atracurium in a renal failure patient.[45] Furthermore, in this study of 20 renal failure patients who received infusions ranging from 38 to 269 hr, no evidence of cerebral excitation occurred. On the other hand, laudanosine may promote seizure activity in susceptible patients as suggested by Griffiths *et al.*[46] The use of haemodialysis is ineffective in eliminating serum laudanosine due to its protein binding and high volume of distribution.[61]

The potential for accumulation of laudanosine is greater in patients with *liver* dysfunction due to its dependency upon hepatic clearance. The clearance and elimination half-life are prolonged in patients with liver failure.[55] It is disconcerting to administer a muscle relaxant continously whose metabolite may cause seizures that may not be clinically detected due to paralysis. Further studies are therefore needed to define the pharmacokinetic behaviour of laudanosine during long-term infusions in critically ill patients with liver and renal dysfunction and what effect, if any, laudanosine has upon cerebral activity.

The other metabolite of Hofmann elimination raising theoretical concerns is the monoacrylate, a highly reactive substance capable of causing alkylation of cellular proteins containing nucleophilic groups, which may lead to cellular dysfunction.[62] However, there are no clinical reports suggesting any ill effects secondary to this reaction. Furthermore, Nigrovic *et al.* suggest that the potential for generation of these toxic end products is probably less than previously hypothesized by original models of atracurium metabolism.[63]

SIDE EFFECTS

Reports have shown that atracurium has little or no cardiovascular effects following single and incremental dose administration sufficient to cause adequate relaxation for intubation and surgical procedures.[58,64–68] However, caution must be exercised during rapid bolus administration which may cause hypotension due to histamine release, particularly in the hypotensive, hypovolaemic or elderly patient. Atracurium has approximately 30% of d-tubocurarine's potential to release histamine which may cause erythema, swelling, bronchospasm, hypotension, tachycardia and anaphylaxis.[69] However, if a bolus injection is administered over one minute the histamine release is reduced.

In summary, atracurium's rapid recovery potential, non-dependency upon renal or hepatic function for metabolism, lack of cumulative effects, and cardiovascular stability during continuous administration, makes it an attractive drug for long-term administration in the critically ill patient.

However, the accumulation of its metabolite, laudanosine, must be considered in a patient with underlying hepatic/renal dysfunction.

Vecuronium

Vecuronium, a derivative of pancuronium, provides good intubating conditions within 90 sec in 90% of patients following a dose of 0.1 $mg \cdot kg^{-1}$.[70] Increasing the dose to 0.4 $mg \cdot kg^{-1}$ reduces the mean onset time to 78 sec with no adverse haemodynamic effects.[71] A dose of 0.5 $mg \cdot kg^{-1}$, in patients undergoing coronary artery bypass grafting, produces excellent intubating conditions with onset times comparable to succinylcholine.[72] Therefore, in conditions where rapid tracheal intubation is desirable, high-dose vecuronium (0.4-0.5 $mg \cdot kg^{-1}$) is an alternative in patients in whom the administration of succinylcholine is contraindicated. However, the duration of action, which is dose-dependent, will be considerably longer, e.g., after a dose of 0.4 $mg \cdot kg^{-1}$, the mean duration of action is 115 min.[71]

Following an intubating dose of 0.1 $mg \cdot kg^{-1}$, the time from injection to 90% recovery of twitch response is approximately 45 min, which is approximately one-quarter the duration of action of pancuronium (Table VI). Antagonism of a vecuronium-induced neuromuscular block, when single twitch has spontaneously recovered to more than 20%, is predictable and effective within minutes following anticholinesterase administration.[73] For more intense blocks, although edrophonium (0.8 $mg \cdot kg^{-1}$) has been shown to have a more rapid onset of action,[74,75] the time to clinical recovery was similar to neostigmine (0.07

$mg \cdot kg^{-1}$) and there were a number of patients with a delayed clinical recovery.[75] For reversal of a profound neuromuscular block induced either by vecuronium or atracurium, neostigmine is more effective.[76]

Several reports have documented a "cumulative" effect of vecuronium following repeated bolus administration.[77–80] Therefore, failure to monitor the intensity of neuromuscular block with a peripheral nerve stimulator and titrating the administration rate accordingly, may result in a prolonged duration of action. Continuous infusions of vecuronium (0.1–0.2 $mg \cdot kg^{-1} \cdot hr^{-1}$) with satisfactory results have been employed mainly during operative procedures. However, use of this technique with critically ill patients has been limited and has produced conflicting results. For instance, studies comparing the pharmacokinetic behaviour of vecuronium in patients with and without renal failure have found no differences.[81–84] However, these studies involved either single bolus administration or short continuous infusion periods (minutes) which does not consider the potential accumulation of vecuronium or its active metabolites during longer infusion periods.[84] In renal failure in patients who received long-term infusions of vecuronium (greater than 24 hr), a partial neuromuscular block persisted for up to 37 hr.[84–86]

Conversely, Darrah *et al.* found no evidence of prolongation of action following continuous infusion of vecuronium for periods of 15 to 68 hr in 13 ICU patients with no renal dysfunction.[87] Furthermore, Coursin *et al.* report two patients who required considerable increases in infusion rates to maintain a steady-state neuromuscular block.[88] It is evident that further study is indicated to examine the vecuronium dosage requirements during long-term infusion and the effects of renal dysfunction upon these requirements.

METABOLISM/EXCRETION

Hepato-biliary clearance is the major route of elimination of vecuronium and accounts for the removal of up to 50% of the injected dose.[89] Since redistribution is responsible for the termination of effect of small doses, no alteration of pharmacokinetic behaviour occurs following an intubating dose of 0.1 $mg \cdot kg^{-1}$ in patients with alcoholic liver disease.[56,90,91] However, the administration of larger doses (0.2 $mg \cdot kg^{-1}$) may result in considerable prolongation of neuromuscular block since elimination (hepato-biliary function) now plays an important role.[92] Prolongation of action is also seen in patients with cholestasis[93] which has been previously documented in cat[94] and rat[95] models. Due to the lack of clinical studies in patients with hepato-biliary dysfunction, inferences regarding alterations in pharmacokinetic behaviour during long-term infusions cannot be made.

Renal clearance accounts for up to 25% of vecuronium excretion as well as its 3-OH metabolite which has neuromuscular blocking activity.[96,97] Accumulation (increase in serum concentrations) of these compounds may account for the prolonged recovery times seen in patients with renal failure. Similarly, whether the "cumulative effect" is a result of accumulation or secondary to a change in the pharmacokinetic behaviour of vecuronium is unknown.

SIDE EFFECTS

Vecuronium has no autonomic ganglion or vagal blocking properties. Doses used for continuous paralysis as well as high-dose bolus administration offer haemodynamic stability.[98–101]

In summary, the relatively short duration of action of vecuronium, its ease of reversal, and cardiovascular stability during its administration are attractive qualities for its use in the ICU. The absence of histamine release during its administration is an indication for its use in patients with hyperactive airways, e.g., asthma. However, the dose must be titrated carefully since there may be changes in drug requirements during long-term administration.

Pancuronium

Pancuronium will produce adequate intubating conditions in 90–120 sec following an intravenous dose of 0.1–0.15 $mg \cdot kg^{-1}$ with a duration of action of approximately 60 min (Table VI).[102] Reversal of blockade can be effectively achieved within 10–15 min when single twitch has spontaneously recovered to 20% of control.[103] The more intense the block, the longer the recovery period and neostigmine is more effective compared to edrophonium and pyridostigmine for reversal of an intense neuromuscular block; however, large doses (0.08 $mg \cdot kg^{-1}$) may be required.[104] A common means of providing long-term paralysis with pancuronium is to administer intravenous boluses of 2–3 mg whenever "the patient begins to move." Although this method reduces the likelihood of significant accumulation, particularly in patients with impaired renal function, it is incapable of providing a continuous adequate level of neuromuscular block. Theoretically, if the indication for the continuous administration of a neuromuscular blocker is to decrease diaphragmatic/thoracic wall muscle activity in order to improve ventilator/patient compliance, this method of intermittent administration may negate its desired effects due to periods of inadequate paralysis. It is therefore more appropriate to administer incremental boluses or a continuous infusion (0.02–0.04 $mg \cdot kg^{-1} \cdot hr^{-1}$) titrated according to the response of the peripheral nerve stimulator.

METABOLISM/EXCRETION

Sixty to eighty per cent of pancuronium and its 3-OH metabolite, which has 50% neuromuscular blockade

potency, are dependent upon renal excretion.[105] As a result, the elimination half-life and duration of action of pancuronium are increased in patients with renal dysfunction.[106] Since they are polar hydrophilic substances, haemodialysis and peritoneal dialysis are ineffective in eliminating these compounds.[107] Hilgenberg *et al.* reported a 195% increase in duration of action in renal failure patients.[102] Berntman *et al.* also reported increases in duration of action following incremental doses of pancuronium (0.015 mg · kg^{-1}) from 40–56 min in 30 normal patients to 65–100 min in 29 anephric patients. They noted not only a disturbing variation in duration of action but also signs of accumulation in anephric patients.[108] The pharmacokinetic behaviour of pancuronium in patients with renal dysfunction predict significant dose reductions.[109]

Increases in elimination half-life have also been demonstrated in patients with acute liver failure,[110] cirrhosis,[111] and total biliary obstruction.[112] Therefore any critically ill patient with compromised liver and/or renal function are at risk for prolonged neuromuscular blockade during pancuronium administration. Furthermore, pancuronium can elicit a "cumulative" effect and therefore if not monitored appropriately, will predispose the patient to prolonged paralysis.[102,109]

SIDE EFFECTS

Pancuronium inhibits reuptake and augments the release of noradrenaline at the adrenergic nerve terminal. As a result, it may augment blood pressure and heart rate which may be a desirable effect in the hypotensive patient. However, one must also be cognizant of the arrythmogenic effects as a result of the increased circulating catecholamines. Furthermore, the effects of increasing myocardial oxygen demands in the patient with coronary artery disease must not be overlooked. Morris *et al.* demonstrated a 24% and 22% increase in mean arterial blood pressure and heart rate respectively, following administration of 0.1 mg · kg^{-1} of pancuronium.[113] Similarly, Gilbert *et al.* have suggested the use of pancuronium during coronary artery bypass surgery may alter the myocardial oxygen balance leading to ischaemia.[114]

In summary, pancuronium's potential for "cumulation" and prolongation of action in patients with renal/hepatic dysfunction and biliary obstruction are disadvantages of its use compared to the other non-depolarizing muscle relaxants available. It must be determined whether or not its sympathomimetic effects will be deleterious, particularly to the patient with coronary artery disease. It has the lowest cost of all intermediate and long-acting muscle relaxants (Table VI) which is an attractive feature for long-term administration. The necessity for careful neuromuscular monitoring during its administration cannot be overemphasized.

New non-depolarizing agents

These agents are scheduled for release in Canada. As such, no cost comparisons can be made. There are no reports of experience with long-term infusions in ICU patients.

Mivacurium

Mivacurium is structurally related to atracurium and following an intubating dose of 0.15 mg · kg^{-1}, provides optimal intubating conditions within two minutes.[115,116] However, its duration of action is much shorter (24 vs 64 min) than atracurium following an intubating dose. The mean time of recovery from 5 to 95% block is 14.4 min.[117] Recovery following a continuous infusion (ranging from 35–324 min) occurred at rates similar to those measured following single bolus administration. The majority of mivacurium is hydrolyzed by plasma cholinesterase resulting in pharmacologically inactive products. However, other routes of metabolism are being examined.[117] Theoretically, prolongation of a mivacurium neuromuscular block should occur in patients with decreased plasma cholinesterase activity and following administration of anticholinesterases. No important cardiovascular effects occur after doses up to 0.15 mg · kg^{-1} but hypotension may occur after higher doses.[116] Like atracurium, the hypotensive effects are abolished if the drug is administered over 60 sec.[118] The pharmacokinetic characteristics of mivacurium offer no advantage for its administration in the ICU over atracurium.

Pipecuronium

Pipecuronium is structurally related to pancuronium and vecuronium and following an intubating dose of 70 μg · kg^{-1} provides optimal intubating conditions within three minutes.[119] Its clinical duration is slightly longer than pancuronium (70 vs 60 min); however, like vecuronium, it does not cause tachycardia or an increase in blood pressures.[120,121] Recovery can be achieved by neostigmine within ten minutes if the block has returned spontaneously to at least 20% of control. Pipecuronium is eliminated primarily by the kidneys (>75%) and a small proportion (<20%) relies on hepatic metabolism. Administration by continuous infusion has not been reported. Its pharmacokinetic behaviour in the ICU patient is likely to be comparable to pancuronium but it is devoid of pancuronium's sympathomimetic effects.

Doxacurium

Doxacurium will produce maximal depression at approximately 6 min following an intubating dose of 0.05 mg · kg^{-1}.[122] Duration of action is 83 min, the longest of all muscle relaxants. Elimination is dependent upon renal (up to 40%) and biliary excretion. The elimination half-life is prolonged in patients with renal and/or hepatic impairment and the duration action has been shown to be prolonged in

TABLE VII Causes of prolonged neuromuscular blockade

1 Excessive drug administration.
2 "Cumulative" drug effect, e.g., pancuronium, vecuronium.
3 ↓ Metabolism/excretion of muscle relaxant, e.g., renal/hepatic dysfunction.
4 Accumulation of active metabolites.
5 Electrolyte imbalances: hypokalaemia, hypocalcaemia, hypermagnesaemia, hypernatraemia.
6 Hypothermia.
7 Drug interactions
- inhalational anaesthetics
- local anaesthetics
- calcium-channel blockers
- antiarrythmics, i.e., quinidine, procainamide
- antibiotics, i.e., aminoglycosides
  - tetracyclines
  - vancomycin, lincomycin
  - clindamycin
- immunosuppressives: cyclosporin

8 Increased sensitivity to muscle relaxants: i.e., neuromuscular disorders; myasthenia gravis, polymyositis.

renal failure patients during general anaesthesia.[123,124] Residual neuromuscular block is readily antagonized most effectively by neostigmine[125] and it is devoid of histamine release or cardiovascular effects following its administration.[122,126,127] Due to its long duration of action, administration of incremental boluses may prove to be an efficient and safe method of maintaining a continuous neuromuscular block in the ICU patient.

Monitoring neuromuscular blockade

The management of the critically ill patient is often complex due to coexisting multiple drug therapy and underlying disease processes which may lead to multi-organ dysfunction and metabolic derangements. As such, there are many variables which may influence neuromuscular transmission (Table VII). Hypothermia increases the intensity of a non-depolarizing neuromuscular block which is attributed to a reduction in plasma clearance and metabolism of the muscle relaxant as well as its direct effect upon neuromuscular transmission.[128,129] Electrolyte disorders may have a considerable impact on neuromuscular transmission. Calcium is required for the release of acetylcholine from the pre-synaptic terminal and the interaction of the actin and myosin filaments.[130] Therefore hypocalcaemia and high serum levels of its competitive inhibitor magnesium, will reduce acetylcholine release and actin/myosin interaction thereby potentiating non-depolarizing neuromuscular block. Sodium competes with calcium at the pre-synaptic terminal;[131] high serum sodium concentrations decrease acetylcholine release resulting in potentiation of non-depolarizing relaxants as well. Respiratory acidosis not only causes potentiation of neuromuscular blockade, but also may impede its antagonism.[132,133] Metabolic acidosis, surprisingly, has little or no effect, but the reasons for this are unclear. Many drugs augment neuromuscular block and it is not unusual to have a patient whose pharmaceutical regimen contains one or more of the drugs listed in Table VII. As a result, the pharmacokinetic and pharmacodynamic characteristics of any drug administered to the critically ill patient are unpredictable. Therefore, it is necessary to monitor the effect of the administration of all muscle relaxants with a peripheral nerve stimulator. A flaccid paralysis (100% muscle end-plate receptor block) induced by a muscle relaxant is not indicated in the critically ill patient except for the purposes of tracheal intubation. A flaccid paralysis increases the risk of an inadvertent administration of an overdose of muscle relaxant since no assessment of neuromuscular block can be made.

Methodology

Train-of-four (TOF) stimulation of a peripheral nerve with a peripheral nerve stimulator (PNS) and monitoring the evoked response, e.g., finger twitch, provides the intensivist with a simple method of monitoring neuromuscular block at the bedside. The capability of reversing neuromuscular block should always exist to allow examination of the patient as required. Continuous neuromuscular monitoring should permit this. Furthermore, each patient's response to a muscle relaxant is unpredictable and the muscle relaxant must be titrated accordingly. As such, the dosage schedules in Table VI are guidelines and are not to be strictly adhered to. We recommend monitoring the evoked response to TOF stimulation every 30 min until a stable state has been achieved. Thereafter, every 1–2 hr is sufficient to prevent prolonged and profound block. If there is no response to TOF stimulation, administration of the muscle relaxant should be discontinued until an evoked response returns. At that time, the infusion or incremental bolus administration may be resumed.

The optimal level of neuromuscular block can be determined by titrating the muscle relaxant, beginning with a low dose, and monitoring its clinical effect. For example, one method of reducing high-peak inspiratory ventilatory pressures is to apply a neuromuscular block to improve ventilatory compliance. Concomitant measurement of peak inspiratory pressures and static/dynamic compliance following increments in the degree of neuromuscular block should demonstrate an optimal level. Improvement in gas exchange has been shown to occur following induction of paralysis in patients with adult respiratory distress syndrome and respiratory failure.[134,135] It is postulated that this improvement was due to a reduction in the work of breathing and an increase in functional residual capacity resulting in an improved ventilation-perfusion match. All patients in this study exhibited considerable muscular

activity prior to the administration of muscle relaxants. Patients who do not exhibit muscular activity during positive-pressure ventilation have no beneficial effect on oxygenation following paralysis.[136]

For assessment of recovery from neuromuscular block, a TOF ratio (amplitude of fourth twitch/amplitude of first twitch) of 0.75 correlates with adequate neuromuscular recovery.[137] However, discrepancies exist between an assessment of the T_4/T_1 ratio, using either visual or tactile estimation, and the degree of neuromuscular block.[138] In the presence of a residual neuromuscular block, the patient with a tracheal tube in place may be capable of eliciting an adequate tidal volume (10–12 ml · kg^{-1}) and of generating a negative inspiratory pressure > 30 cm H_2O yet, following extubation, the patient is incapable of maintaining a patent airway due to weakness of the upper airway muscles. Therefore, we should not rely solely on the evoked response to TOF stimulation and use other clinical variables (e.g., strong hand grip, capability of raising the head for five seconds, and ability to protrude the tongue) as indicators of adequate recovery.[139,140]

A variety of electrodes is available for use with peripheral nerve stimulators, e.g., needles, probes, plates. However, the pregelled ECG surface electrodes remain the most efficient. They are disposable, noninvasive, self-adhering, and comfortable. The skin is best prepared by scraping off excess keratin using the granite surface located on the electrode cover and cleaning the area with alcohol. The electrodes should be replaced every 24 hr, and earlier if necessary, due to gel decomposing, patient sweating, or any other factors affecting the electrode contact with skin. The negative pole (usually coloured black) is the stimulating electrode and is placed directly over the nerve and the positive red electrode is placed in the near vicinity. The PNS should be capable of generating up to 60 mA current otherwise inadequate stimulation of the nerve may occur causing overestimation of the degree of neuromuscular block. In particular, current density decreases rapidly as the distance between the stimulating electrode and the nerve increases. Therefore, the patient who develops peripheral oedema will require a higher stimulating current to elicit an evoked response.[141] Several peripheral nerve sites have been used for this purpose; however, the ulnar and median nerves are the most popular. Furthermore, differences in sensitivity to muscle relaxants exist among different peripheral muscle groups, e.g., the facial nerve/muscle group underestimates the degree of neuromuscular block compared to ulnar nerve stimulation.[142] Thus, stimulation of either the median or ulnar nerve and monitoring the evoked response in the innervated muscle are the most accurate sites to determine adequate recovery of neuromuscular block. If these nerves are inaccessible, alternative sites such as the posterior tibial or peroneal nerves are recommended. Stimulation of the facial nerve is uncomfortable and should not be attempted in the awake patient.

In summary, the complex nature of the critically ill patient may alter the pharmacokinetic and pharmacodynamic characteristics of any drug administered. Therefore, administration of a muscle relaxant must be titrated to a desired clinical effect (patient benefit) using a peripheral nerve stimulator. Also, the clinician must be aware of the possible side effects of the muscle relaxant (patient risk) in order to minimize patient morbidity. Muscle relaxants, when administered appropriately, may optimize mechanical ventilation thereby improving oxygenation and ventilation in the critically ill patient.

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