

Neuromuscular blocking drugs in the critically ill

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Neuromuscular blocking drugs (NMBDs) are now used less frequently in critically ill patients than they were 15 years ago, mainly because of improved techniques of artificial ventilation.¹ Some indications for their use are given in Table 1.² It is inappropriate to extrapolate experience with the use of NMBDs in the operating theatre in healthy patients to the management of the critically ill. These sick patients often have multiple organ failure and are receiving concomitant medications. The pharmacokinetic and pharmacodynamic properties of NMBDs in this population are poorly understood. There have been repeated reports of prolonged neuromuscular block after long-term administration of NMBDs in the critically ill as a result of overdosage, prolonged excretion of the NMBD and its metabolite, or critical illness myopathy.²

The ideal NMBD for use in the critically ill would be disposed of independently of renal or hepatic function; have no adverse cardiovascular effects; produce no metabolite with neuromuscular blocking activity; not interact with other drugs or accumulate over time; have a rapid and predictable onset and offset of effect; and be of low cost.² No presently available agent meets all these requirements.

Depolarizing agents

Succinylcholine

Succinylcholine (1.0–1.5 mg kg⁻¹) produces the most rapid onset of neuromuscular block of all NMBDs (60 s). It is hydrolysed by plasma cholinesterase and its clinical duration of action is up to 12 min. Factors affecting its metabolism are shown in Table 2.³

The side-effects of succinylcholine include hyperkalaemia, malignant hyperpyrexia, bradyarrhythmias, increase in intraocular/intragastric/intracranial pressure, and a higher risk of anaphylaxis than with other NMBDs. It is relatively contraindicated for use in patients with sepsis, massive trauma, burns, spinal cord transection, CNS injuries/infections, prolonged immobilization, disuse

Table 1 Indications for the use of NMBDs in the critically ill. (derived from ref. 2)

- Facilitation of mechanical ventilation and to aid oxygenation, e.g. in adult respiratory distress syndrome by
 - improving chest wall compliance
 - reducing peak airway pressure
 - preventing incoordinate respiratory movements
 - prone ventilation
- Facilitation of tracheal intubation
- Control of increases in intracranial pressure, e.g. after head injury, neurosurgery
- Reduction of muscle tone
 - Tetanus
 - Neuroleptic malignant syndrome
 - Status epilepticus
- Facilitation of procedures and tests
 - Inter-hospital and intra-hospital patient transport
 - Bronchoscopy, tracheostomy
 - MRI, CT scanning

atrophy, Guillain-Barré syndrome and peripheral nerve injury, because of the risk of an exaggerated and potentially fatal increase in serum potassium.⁴ Denervation or burn injury leads to hypersensitivity to succinylcholine as a result of motor endplate receptor multiplication. This is thought to be the explanation for the hyperkalaemic response, which is evident by 3–5 days after the insult and peaks at 7–8 days.⁴ The response can occur even in a critically ill patient with normal renal function and a normal plasma potassium concentration before the succinylcholine is given. Succinylcholine should be avoided if at all possible in the critically ill.

Non-depolarizing agents

Aminosteroids

Pancuronium

Pancuronium is a long-acting NMBD. It produces adequate intubating conditions in 2.5–3.0 min after a dose of 0.1–0.15 mg kg⁻¹. Pancuronium (60–80%) and its 3-OH metabolite, which has at least 50% of the neuromuscular blocking potency of the parent compound, are dependent upon renal clearance. The elimination half-life and duration of action of pancuronium are increased in patients with renal dysfunction. An increase

Key points

NMBDs are now less frequently required to manage the critically ill patient.

Neuromuscular block should be monitored if relaxants are used in these patients.

Succinylcholine can cause cardiac arrest from hyperkalaemia in the critically ill.

Repeated doses or infusions of neuromuscular blocking agents can cause prolonged muscle weakness in patients who are artificially ventilated for several days.

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in elimination half-life has also been demonstrated in patients with acute liver failure, cirrhosis and total biliary obstruction. Any critically ill patient with compromised liver and/or renal function is at risk of prolonged neuromuscular block after pan-

Table 2 Pathophysiological changes which potentiate the action of NMBDs in the critically ill³

- Acid–base disturbances
 - Metabolic acidosis
 - Respiratory acidosis
 - ? Metabolic alkalosis
 - Hypothermia
- Electrolyte imbalance
 - Hypokalaemia (hyperpolarizes muscle membrane)
 - Hypernatraemia (hyperpolarizes muscle membrane)
 - Hypocalcaemia (decreases presynaptic acetylcholine release)
 - Hypermagnesaemia (decreases presynaptic acetylcholine release)
- Drug interactions
 - *Succinylcholine* is potentiated by:
 - Inhibitors of plasma cholinesterase e.g. neostigmine, organophosphorous compounds e.g. ecothiopate, ester local anaesthetic agents, metoclopramide, hexafluorenum, alkylating agents e.g. cyclophosphamide, trimetaphan, esmolol, etomidate
 - Decrease in effective plasma cholinesterase, e.g. homozygous atypical plasma cholinesterase, pregnancy, liver disease
 - *Non-depolarizing NMBDs* are potentiated by:
 - Calcium channel blockers, e.g. verapamil, diltiazem
 - Antibiotics, e.g. aminoglycosides (neomycin, gentamicin, vancomycin, kanamycin), erythromycin, tetracycline, lincomycin, clindamycin, metronidazole
 - Local anaesthetic agents, quinidine
 - Immunosuppressant drugs, e.g. cyclosporine, azathioprine
 - H₂ receptor antagonists
 - Trimetaphan
 - Lithium carbonate
- Pre-existing neuromuscular disease
 - Myasthenia gravis
 - Myasthenic syndrome
 - Muscle disorders, e.g. muscular dystrophy, myotonia, familial periodic paralysis, poliomyelitis

curonium. There is a recent report of prolonged (>10 h) neuromuscular block after cardiac surgery in two patients after using a pancuronium infusion for 5 h.⁵ Both the patients had mild renal impairment and had received large doses of pancuronium. Pancuronium is no longer indicated for use in the critically ill. Its sympathomimetic effects are also disadvantageous in such patients.

Vecuronium

Vecuronium is an intermediate-acting NMBD. It provides good intubating conditions within 2.5 min after a dose of 0.1 mg kg⁻¹. It is a derivative of pancuronium and is mainly eliminated by the hepatobiliary route (50%). Renal clearance accounts for up to 25% of the excretion of vecuronium. Its 3-OH metabolite has at least 50% of the neuromuscular blocking activity of the parent drug. Figure 1 shows the plasma concentrations of vecuronium and its active metabolite (3-desacetylvecuronium) in a critically ill patient after stopping a vecuronium infusion which had been administered for 6 days.⁶ This patient was admitted to intensive care with respiratory failure from *pneumocystis carinii* pneumonia. The patient had recently had a cadaveric renal transplant and was receiving azathioprine, cyclosporine A and prednisone for immunosuppression. The patient was given pancuronium (total 22 mg in the first 34 h of paralysis) followed by a vecuronium infusion for the next 6 days (total of 337 mg) to improve ventilation and maintain oxygenation. Neuromuscular block was not monitored and the patient had three episodes of haemodialysis during the infusion. It was 3 days after stopping the vecuronium infusion before the drug was barely detectable in the plasma, and the active metabolite was still detectable 8 days after stopping it (Fig. 1). There have been several reports of prolonged neuromuscular block (up to 7 days) after infusions of vecuronium

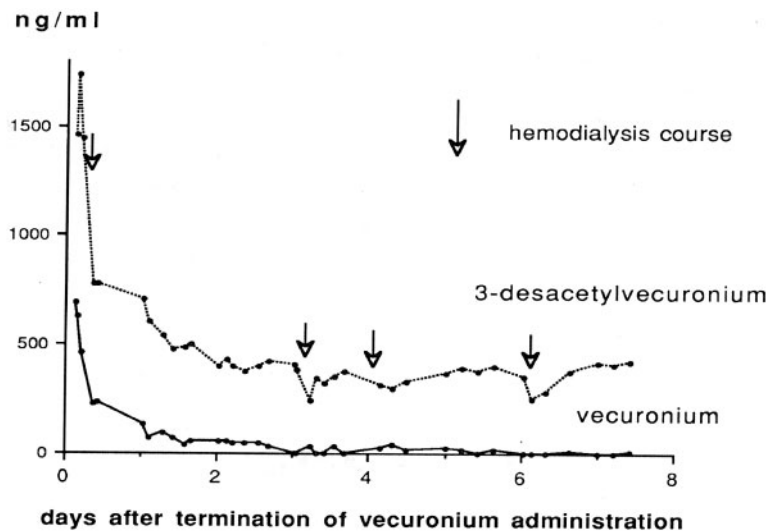


Fig. 1 Plasma concentrations of vecuronium (solid line) and 3-desacetylvecuronium (dotted line) in a critically ill patient after stopping a 6 day vecuronium infusion at time zero.⁶ (Published with permission from Lippincott, Williams & Wilkins.)

Table 3 Pharmacokinetics of the NMBDs commonly used in the critically ill⁷

NMBD	Volume of distribution (Vd _{ss}) ml kg ⁻¹		Plasma clearance (Cl) ml kg ⁻¹ min ⁻¹		Elimination half-life (t _{1/2β}) min	
	Healthy	ITU	Healthy	ITU	Healthy	ITU
Vecuronium	152	494	5.4	2.6	34	173.9
Atracurium	202.1	203.2	6.6	8.9	20.9	23.4
Cisatracurium	161	316.5	5.7	7.9	30.0	27.6

in the critically ill. There is little indication for its use in such patients: the pharmacokinetics of vecuronium are deleteriously altered in these cases (Table 3).⁷

Pipecuronium

Pipecuronium is structurally related to pancuronium and vecuronium. After an intubating dose of 70 µg kg⁻¹, it provides optimal intubating conditions within 3 min. It is eliminated primarily by the kidneys (>75%), and a small proportion (<20%) undergoes hepatic metabolism. Its pharmacokinetic behaviour in the critically ill is likely to be comparable with pancuronium, but it is devoid of the sympathomimetic effects of the older drug. It is not available for use in the UK.

Rocuronium

Rocuronium is similar in structure to vecuronium and shares its properties of cardiovascular stability and minimal histamine release. In doses of 600 µg kg⁻¹, it provides adequate intubating conditions in more than 95% of patients at 75 s. The onset is more rapid than with any other non-depolarizing agent and almost as quick as with succinylcholine. The duration of action of rocuronium is similar to vecuronium. It is mainly eliminated by the liver, and is also excreted in the urine. Its metabolite (17-desacetylrocuronium) has only 5% of the neuromuscular blocking activity of the parent drug, which has no clinical significance. Rocuronium offers no advantage over vecuronium except in bolus doses (0.6–0.9 mg kg⁻¹) for tracheal intubation in the critically ill, especially when succinylcholine is contraindicated.

Benzylisoquinoliniums

d-Tubocurarine

d-Tubocurarine was the first non-depolarizing agent to be used in the critically ill.³ A dose of 0.5–0.6 mg kg⁻¹ is required for intubation and it is slow in onset. It is not metabolized in the body. Most of it is eliminated via the kidneys with some excretion (12%) in the bile. d-Tubocurarine causes hypotension as a result of histamine release and a degree of autonomic ganglion blockade. There is no indication for its use in the critically ill.

Alcuronium

Alcuronium is two to three times more potent than d-tubocurarine. It has a slower onset of action after an

intubating dose of 0.2 mg kg⁻¹. This drug is not metabolized in the body and its histamine releasing capacity is less than with d-tubocurarine. Alcuronium is excreted unchanged in urine. It has a similar ability to cause anaphylaxis to succinylcholine. There is no place for using it in the critically ill.

Atracurium

Atracurium 0.5–0.6 mg kg⁻¹ produces adequate conditions for tracheal intubation within 2.5 min. Clinical recovery occurs in about 20–30 min. Atracurium is disposed of by *Hofmann elimination*—spontaneous degradation in the plasma at physiological pH and temperature into laudanosine and a mono-quaternary acrylate. Ester hydrolysis also contributes to its disposition. It does not depend on renal or hepatic function for its elimination. The onset and duration of effect of atracurium are predictable, however sick the patient. These properties make it useful for managing the critically ill patient.

Cisatracurium

Cisatracurium is the 1R-*cis* 1'R-*cis* isomer of atracurium. It is up to five times as potent as atracurium and hence a smaller dose is required for intubation (0.1 mg kg⁻¹). Its onset time is longer than for atracurium (3 min). Hofmann degradation is the main route of its disposition and ester hydrolysis is less important than with atracurium. It releases less histamine than atracurium. The pharmacokinetic profiles of atracurium and cisatracurium are similar in the critically ill to healthy patients (Table 3).⁸

Laudanosine controversy

Laudanosine is the breakdown product of Hofmann degradation of atracurium and cisatracurium. It has epileptiform effects in animals. The peak plasma laudanosine concentration after a bolus dose of atracurium 0.5–0.6 mg kg⁻¹ is ~0.2 µg ml⁻¹. The plasma concentration of laudanosine after an equipotent dose of cisatracurium is about one-fifth of that after atracurium. Plasma concentrations of laudanosine after continuous infusion of atracurium for several hours (even days) in the critically ill are <5.1 µg ml⁻¹.⁹ However, there is one report of a laudanosine concentration of 20 µg ml⁻¹ after 72 h of infusion of atracurium.¹⁰ Further breakdown of atracurium *ex-vivo* in the plasma cannot be discounted in this report. The laudanosine concentration required to cause seizures in dogs is 17 µg ml⁻¹. There are no known reports of seizures in humans caused by laudanosine.

Mivacurium

Mivacurium is structurally related to atracurium. After an intubating dose of 0.15 mg kg⁻¹, it provides optimal intubating conditions within 3 min. Recovery after continuous infusion occurs at rates similar to those measured after single bolus administration. The majority of mivacurium is hydrolysed by plasma cholinesterase resulting in pharmacologically inactive products. As with succinylcholine, prolongation of mivacurium-induced neuromuscular block may occur in patients with

decreased plasma cholinesterase activity attributable to inherited or acquired causes (Table 2). The pharmacodynamic and pharmacokinetic properties of mivacurium provide no advantage over other NMBDs in the critically ill.

Doxacurium

Doxacurium only provides optimal intubating conditions in 6 min after an intubating dose of 0.05 mg kg⁻¹. Its clinical duration of action is over 80 min, the longest of all NMBDs. However, it does not stimulate histamine release or have adverse cardiovascular effects. Elimination is dependent on renal (up to 40%) and biliary excretion. The elimination half-life is prolonged in patients with renal and/or hepatic impairment. There are no indications for its use in the critically ill.

Monitoring of neuromuscular block

Neuromuscular block should be monitored in all critically ill patients receiving NMBDs by continuous infusion. This assessment is usually accomplished using peripheral nerve stimulation and clinical assessment. A survey of ITU practitioners in 1992 suggested that most patients requiring prolonged administration of NMBDs were not being monitored with a peripheral nerve stimulator.¹¹ Even clinical assessment of neuromuscular block by visual or tactile means only has its limitations.² It has not been demonstrated that such monitoring reduces the risk of prolonged paralysis in the critically ill. Nevertheless, it is advised that at least a train-of-four (TOF) count be recorded 1–2 hourly on the intensive care unit (ICU) chart in all patients receiving NMBDs, if the TOF ratio cannot be measured by the monitoring equipment in use. The TOF Watch SX is suitable for such purposes, as this allows the TOF ratio to be recorded.

Prolonged neuromuscular block

Numerous case reports describe prolonged and persistent muscle weakness after the use of NMBDs in critically ill patients. It has been reported more commonly after the use of aminosteroidal agents.⁷ However, the older benzylisoquinoliniums and mivacurium, atracurium and cisatracurium have also been associated with persistent muscle weakness.⁷ One study estimates a 5–10% risk of developing prolonged weakness if NMBDs have been used for more than 24 h.¹² The cause of muscle weakness in the critically ill is multifactorial. It may occur even when NMBDs have not been given. It is important to distinguish between prolonged neuromuscular block from drug overdosage or the effect of drug metabolites, and critical illness neuromyopathy. Associated factors include immobility, protein catabolism, sepsis, asthma and steroid use.

Overdosage

Overdosage and long-term use of NMBDs may result in the accumulation of parent drug or its active metabolites.⁶ Over

time, peripheral compartments become saturated and clearance of the drug is decreased. The drug is stored in the basement membrane of the neuromuscular junction, which then acts as a reservoir. Electrolyte and metabolic derangements may potentiate the neuromuscular block (Table 2). Hypothermia has been reported to prolong recovery from pancuronium, vecuronium and atracurium. Even a slight reduction in core temperature (2–3°C) nearly doubles the duration of action of vecuronium and atracurium.

Drug interactions

Drug interactions may also potentiate the effect of NMBDs (Table 2). A number of antibiotics enhance their effect. This is attributed to inhibition of presynaptic acetylcholine release, stabilization of the postsynaptic membrane, or a mixture of pre- and postsynaptic effects.³ Magnesium has both presynaptic and postsynaptic effects at the neuromuscular junction. Drugs such as lidocaine, β -blockers and calcium channel blockers can potentiate neuromuscular block by directly affecting ion transport at the neuromuscular junction. Lidocaine in large doses can reduce the force of muscle contraction by causing a muscle membrane stabilizing effect. All these factors can prevent antagonism of neuromuscular block by neostigmine or calcium.

Pathological defects in the motor unit

These can occur in the muscle, peripheral nerve, and at the neuromuscular junction in the critically ill. They probably start within a few days of commencing artificial ventilation. A high incidence of myopathy (up to 50%) and neuropathy (up to 70%) has been reported in such patients.² Some consider these two phenomena to be part of the same pathological process.

Myopathy

Myopathy in the critically ill has been described in various terms, for example critical illness myopathy and acute myopathy of intensive care, acute quadriplegic myopathy, acute necrotizing myopathy. Clinical examination shows flaccid paralysis with diffuse weakness affecting both proximal and distal muscle groups equally. Deep tendon reflexes are usually present (two-thirds of patients). Nerve conduction studies demonstrate normal sensory amplitudes with low or normal motor amplitudes. Weaning from artificial ventilation is often delayed because of respiratory muscle weakness. Most of the patients who survive the critical episode recover within about 4 months, but some have permanent neurological deficit.

Neuropathy

Neuropathy in the critically ill patients can be either sensory or motor, leading to persistent muscle weakness. It is termed critical illness polyneuropathy. As in myopathy, both proximal and distal group of muscles are affected but the deep tendon reflexes are absent in the majority of these patients. Nerve conduction studies

show that the amplitudes of both the compound muscle action potential and the sensory nerve action potential are decreased. Peripheral nerve biopsy shows primary axonal degeneration of motor and sensory fibres. The overall prognosis is good.

Neuromuscular junction

Neuromuscular junctions can be both structurally and functionally altered in the critically ill.² Conditions such as spinal cord injury, immobilization and burns can result in an increased number of postsynaptic nicotinic receptors. Structurally, these receptors differ from normal acetylcholine receptors, being of the fetal type with a gamma subunit rather than the adult type with an epsilon subunit. They occur extrajunctionally. Functionally, they have a shorter half-life, are more sensitive to depolarizing NMBDs, and more resistant to non-depolarizing NMBDs. The relationship between these changes and the development of prolonged muscle weakness is not clear.

Complications in the ICU

Ensuring adequate sedation in a paralysed patient is essential. An inadequately sedated but paralysed patient may subsequently suffer serious psychological and emotional stress. Use of NMBDs can also result in unrecognized patient-ventilator disconnection especially when less sophisticated ventilators are used.² NMBDs suppress the cough reflex, which results in retention of secretions, atelectasis and pulmonary infection, unless measures to counteract these complications such as physiotherapy are used. Prolonged immobility of the patient is associated with substandard care, increasing the risk of deep vein thrombosis, pulmonary emboli, peripheral nerve injuries, skin breakdown and static ulcers. NMBDs ablate abdominal rigidity and thus the diagnosis of acute abdominal infection or perforation may be delayed in these patients. Neurological examination is not possible in a paralysed patient, which can be a disadvantage in neurosurgical practice. Use of NMBDs can also result in subluxation of unstable spinal fractures.⁴

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Please see multiple choice questions 20–24.