PARALYTIC THERAPY AND COMPLICATIONS IN THE ICU

INTERNAL MEDICINE GRAND ROUNDS

UNIVERSITY OF TEXAS SOUTHWESTERN MEDICAL CENTER
DALLAS, TEXAS

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JANUARY 28, 1999

This is to acknowledge that W. Douglas Pitcher, M.D. has disclosed no financial interests or other relationships with commercial concerns related directly or indirectly to this program.

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The earliest neuromuscular blocking agent (NMBA) is curare ,which is a generic term for the crude plant extracts used for centuries as an arrow poison by South American tribesmen of the Amazon and Orinoco River basins (163). Griffith and Johnson reported the first series promoting the use of NMBA during general anesthesia in 1942 (163). The use of NMBA in the ICU setting was largely an outgrowth of the anesthesiology experience in the operating room (OR). Guidelines and recommendations for the use of NMBA in the ICU have been developed which rely heavily on their use in the OR (38,45,84,87,150) or which rely on surveys of their use by anesthesiology intensivists (95), by academic training programs for pulmonary/critical care (76), or by critical care nurses (111). To some extent this may be justifiable, however, there are numerous differences between the OR and the intensive care unit which have caused some to thoughtfully warn that this extrapolation may have given us "more than we bargained for" (75).

Although some operations may last for many hours, the total duration of NMB is quite short in comparison to the ICU, where these agents may be used for days or weeks. Recovery times and clinical effects are most often described during the distribution phase of the drugs' pharmacokinetics (e.g. after a single bolus) for surgical patients, whereas recovery from NMB in the ICU almost always occurs in the elimination phase. ICU patients are by definition sicker, more unstable, and far more likely to be afflicted with conditions which significantly alter the onset (e.g. low cardiac output or arterial blood pressure), volume of distribution (e.g. anasarca, ascites), or drug elimination and/or metabolism (e.g. renal or hepatic impairment). Surgical patients often are receiving volatile anesthetic agents, the majority of which potentiate NMB activity. Tachyphylaxis occurs with prolonged ICU use of all NMBA. Critical care patients are far more likely to be receiving concomitant treatment with multiple drugs that may have important drug interactions. Furthermore, NMBA may be used in emergent situations where important co-morbid illnesses, electrolyte disorders, or complications may not be known or which may develop during the course of their use. In addition, it is not clear that the same degree of NMB is either necessary or relevant for ICU patients, nor that the same techniques of NMB monitoring are appropriate.

The selection of individual agents as well as the general safety profile of NMBA in the ICU are decidedly different from the OR experience.

Indeed, complications of prolonged muscular weakness following use of NMBA were largely unheard of in the OR literature (11,140). However, after their use in the ICU became commonplace, reports of such complications began to emerge (20,89,99,110,122,146,157,165,185). These reports have continued to accumulate, implicating virtually all NMBA in a variety of clinical situations (8,27,50,68,69,71,79,80,98,100,103,112,113,117,123,129,141,148,151,161,166,180). Though some of these reports showed prolongation of NMB of only several hours, many described cases of protracted quadriparesis prolonging mechanical ventilation by several weeks and requiring many months for rehabilitation and recovery.

Between 1 and 10% of patients treated with mechanical ventilation receive NMBA for more than 24 hours (38). The incidence of prolonged weakness secondary to NMBA has been estimated to be 5% of all such patients (122). The incidence may be as high as 40-45% in patients with asthma treated with steroids and NMBA (50,151) and as high as 30-70% in patients with ARDS and multiple organ dysfunction (17,148,180). One report suggests that the economic impact of a single episode of prolonged weakness from use of NMBA is in excess of $66,000 (143). The use of NMBA may add over $300 per day to the cost of ICU care due to direct drug costs (32).

NMBA use may significantly add to morbidity and cost in ICU patients.

GENERAL PHARMACOLOGY

Neuronal transmission to the neuromuscular junction causes release of acetylcholine (AC) from the presynaptic nerve ending. Binding of AC to the postsynaptic receptor causes depolarization of the muscle membrane, calcium release from the sarcoplasmic reticulum, activation of actin/myosin, and muscle contraction. AC is rapidly cleared from the neuromuscular junction by AC esterase and choline is taken up by the presynaptic neuronal cell for resynthesis of AC. The myocyte restores its resting transmembrane potential and resequesters calcium within the sarcoplasmic reticulum. All NMBA act at the postsynaptic AC receptor. NMBA are usually classified based upon (1) whether or not they cause depolarization of the muscle membrane and (2) their duration of action. Succinylcholine is the only clinically relevant depolarizing NMBA. Binding of succinylcholine results in depolarization of the muscle membrane, and thus actually causes ionic shifts (both intra- and extra-cellular) and muscle contraction. These events initially occur in sporadic muscle fibers, producing fasciculations. Succinylcholine is not broken down by acetylcholinesterase but is cleared by plasma cholinesterase only after it diffuses to the peripheral circulation. Prolonged binding prevents restoration of the transmembrane potential and calcium re-accumulation in the sarcoplasmic reticulum and thus renders the muscle unresponsive to subsequent stimulation, resulting in flaccid paralysis (84).

All other clinically relevant NMBA are non-depolarizing agents which produce paralysis through competitive inhibition of AC. These drugs do not produce muscle depolarization, ion flux, or contraction. Thus, the paralysis develops incrementally as the drug concentration increases and the muscle will remain flaccid and unresponsive to presynaptic stimulation as long as sufficient drug remains within the neuromuscular junction. Because the muscle is not depolarized by these NMBA, it can still contract with direct stimulation. The paralytic effect is confined to peripheral, striated skeletal muscle; none of the NMBA affect smooth muscle or myocardium directly. Some of the side-effects NMBA are related to the varying propensity of various agents to bind to other cholinergic receptors, e.g. producing histamine release or vagolytic effects.

Succinylcholine is also the only short-acting agent for potential use in the ICU. It has a rapid onset (1-2 minutes) and short clinical duration (2-6 minutes), and thus is used exclusively for airway intubation. Although mivacurium is also classified as short-acting (clinical duration 10-20 minutes), its longer onset and tendency to produce significant histamine release with rapid bolus limit its utility for emergent intubation; its very high cost currently precludes its use for sustained continuous infusion.

Most of the non-depolarizing NMBA in use in ICU settings have an intermediate (30-60 minutes) clinical duration of action and are thus best suited for sustained neuromuscular blockade via continuous infusion. The drugs in this group which will be considered in some detail include vecuronium, rocuronium, atracurium, and cisatracurium. Pancuronium is the only currently used NMBA which is classified as long-acting (clinical duration 1½ to 2 hours after single dose). It is a non-depolarizing NMBA which was the first to gain widespread use in the ICU setting.

Paralytic potency for NMBA is expressed as the dose of the drug which produces 95% reduction in the muscle twitch response to supramaximal stimuli (ED_{95}).

The ED_{95} approximates the level of paralysis required during abdominal surgery. While this method is useful for comparative purposes, it has important limitations. The ED_{95} has traditionally been determined under conditions of elective surgery. Since succinylcholine and inhalational anesthetic agents potentiate the activity of NBNA (84,145), the ED_{95} is ideally measured in patients who have been intubated without paralysis and using other non-volatile anesthetic agents (such as short-acting barbiturates along with benzodiazepine pre-medication). 95% single twitch suppression of

the adductor pollicis is analogous to the same response of the abdominal and limb muscles, and thus the ED_{95} is a fair approximation of the clinical response desired for abdominal surgery. However, different muscle groups have varying responsiveness to a given dose of NMBA; the muscles of the larynx, the diaphragm, and the orbicularis oculi are all more resistant to NMBA (25,48,49). The relative resistance of the diaphragm is enhanced in patients with critical illness (134). Thus, it cannot be assumed that the ED_{95} is representative of the dose required to produce other desired clinical endpoints, especially in the ICU.

Despite these limitations, the ED_{95} serves as a useful point of reference for comparing NMBA, especially when examining the onset and duration of drug activity. Doses are usually expressed as a factor of the ED_{95}, e.g. 2 X ED_{95}. There is a fair correlation between the administered dose and both onset and duration of effect. For example, the time to 90% blockade with cisatracurium can be shortened from 3.3 to 1.6 minutes by increasing the dose from 2 X ED_{95} to 5 X ED_{95}, but the duration of action is prolonged from 64 to 97 minutes at these two doses.

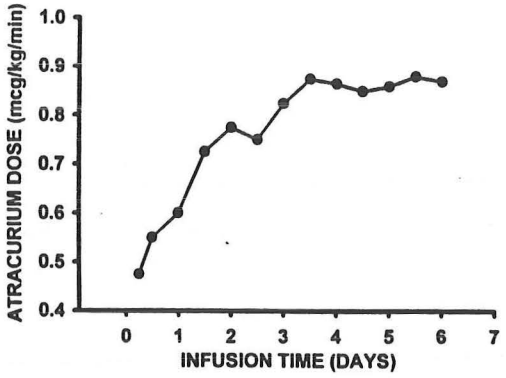
Neuromuscular diseases (16,64) and hypothermia (85) potentiate the action of NMBA. Acute electrolyte disorders including hypermagnesemia (as during treatment for eclampsia), hypokalemia, and respiratory acidosis tend to potentiate non-depolarizing NMBA whereas respiratory alkalosis and hyperkalemia tend to be suppressive (45,85,87). Lithium reduces presynaptic AC release and thus enhances NMBA. Chronic electrolyte changes have little effect, if any.

The volatile anesthetics potentiate NMBA activity, with enflurane having the greatest effect, followed by isoflurane and halothane (145). A wide variety of antibiotics potentiate NMBA, especially the aminoglycosides, but also tetracyclines and macrolides (155,156,181). Other antibiotics reported to have minor effects on NMB include polymyxin, penicillins (156), and metronidazole (39). Lidocaine potentiates NMBA, as does quinidine, propranolol, and calcium channel blockers (45,85,87). Phenytoin (70) and cimetidine (121) have been reported to enhance NMBA, whereas theophylline may be antagonistic (47). In general, the magnitude of these agents' effects on NMBA is small and individual drug contributions to NMBA are likely of little clinical consequence. However, these interactions serve to demonstrate the potential for cumulative effect in critically ill patients receiving numerous drugs and experiencing acute changes in electrolyte status.

All NMBA commonly used in the ICU exhibit tachyphylaxis when used for prolonged NMB.

Most ICU patients have increased dosing requirements over time, especially if they require NMB for more than 48 hours (32,37,133,168). This effect occurs even when careful monitoring with electrical nerve stimulation is followed (32,37,133,168). This likely occurs because chemical muscle denervation leads to up-regulation of postsynaptic AC receptors at extrajunctional sites (23). This effect can be quite significant. Pancuronium dosing may increase the least (22%), but the reported experience in this regard for ICU patients using continuous infusion is limited by small numbers of patients and the fact that in most cases patients have been switched to intermediate duration NMBA after about 2 days of its use (32). Vecuronium has demonstrated the most pronounced tachyphylaxis. The average increased dosing requirements are 93-130% (32,133) and maximal requirements can be up to 540-600% above baseline rates (37). Atracurium is associated with more pronounced early dosing requirements, averaging 45% above baseline infusion at 48 hours, though maximal requirements average about 93% (32). Cisatracurium generally has shown the least tachyphylaxis with an average increase of only 4%, but maximal increases may be 175% (32). The phenomenon of tachyphylaxis with NMBA supports the observation that the ICU experience is different from the OR. It also emphasizes the need for frequent assessment of

dosing requirements and the need to use average dosing requirements when comparing daily costs of individual agents.

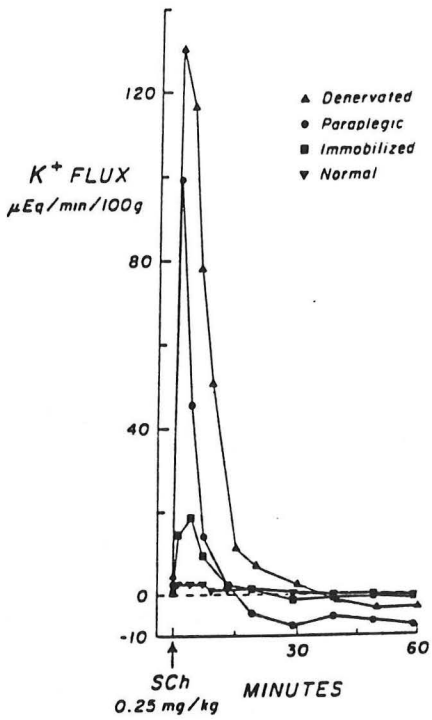


Because non-depolarizing NMBA act through competitive inhibition at the AC receptor site, they can be variably reversed after cessation of drug administration by agents which increase AC concentrations in the neuromuscular junction such as neostigmine or edrophonium (84). Isolated use of either of these agents may lead to undesired effects, most notably those of unopposed cholinergic stimulation. As such, reversal of NMB has traditionally required the concomitant use of cholinergic blocking agents such as atropine or glycopyrrolate (63,91). While the use of these agents may be clinically useful in the recovery phase after anesthesia, their use in ICU patients is very limited. For one, their effect may only enhance recovery by minutes to hours, and the effect is often only transient (35). Thus, it is doubtful that such therapy is of therapeutic benefit. While transient improvement in motor strength may demonstrate that weakness is due to prolonged NMB, this same information can be determined either through use of electrical stimulation ("train-of-four" monitoring) or formal neuro/electromyography.

ICU NEUROMUSCULAR BLOCKING AGENTS

Succinylcholine is associated with a number of complications which derive from its membrane depolarizing effects. The initial fasciculations and dyscoordinated muscle fiber contractions that follow depolarization my produce extracellular release of potassium, phosphate, and myoglobin. Normally this is of little clinical consequence; the plasma potassium concentration increases by about 0.5 mEq/L (14). However, the hyperkalemic response may be far greater (with increases of up to 4 mEq/L) and produce fatal arrhythmias in patients who have sustained significant trauma (15) or extensive burns (164). Patients with denervating neurologic diseases are particularly prone to this phenomenon, so that the drug should not be used in patients with spinal cord injury, extensive peripheral neuropathy, Guillain-Barre, etc. The hyperkalemic response is usually not present initially (e.g. immediately after spinal or burn injury), is significant within 48 hours, tends to peak 2 to 3 weeks later, and likely persists indefinitely (14,84,164). It is thought that these responses are mediated by up-regulation of extra-junction AC receptor density on muscle membrane. As mentioned earlier, this results in tachyphylaxis with non-depolarizing agents, but with succinylcholine the muscle becomes hypersensitive. Muscle denervation appears to be the most important stimulus for receptor up-regulation. In canine studies, succinylcholine administered to immobilized muscle produces a significant potassium efflux compared to normal, however, the response with denervated or paraplegic muscle is 5 to 6 fold greater than with immobilized muscle (74).

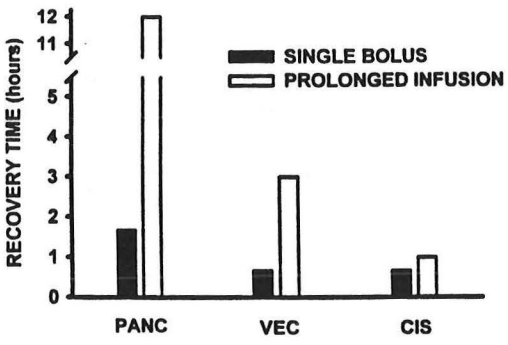
Succinylcholine is one of several agents (e.g. halothane) which can trigger malignant hyperthermia (28,73), a peripheral disorder which is associated with altered calcium transfer across the sarcoplasmic reticulum. Although this is rare (1 in 50,000), it has a hereditary predisposition and may occur more frequently in patients with muscular dystrophy (154). Patients develop rapid, extreme hyperpyrexia, hypermetabolism, acidosis, muscle rigidity, rhabdomyolysis, and hemodynamic lability. In severe cases there may be evidence of DIC or renal failure (14). Most cases can be managed with supportive care and dantrolene. It is likely that this syndrome is rarely, if ever, triggered by the non-depolarizing NMBA; in fact, pretreatment with non-depolarizing NBBA can prevent succinylcholine induced malignant hyperthermia in swine (73). NMBA are not thought to be triggers for the neuroleptic malignant syndrome (NMS) which has similar clinical features; this is a central disorder of dopaminergic receptors which most commonly follows use of neuroleptic drugs and which does not respond to dantrolene. Indeed, NMBA have been described as adjunctive measures to control muscle rigidity in NMS (146).



Plasma cholinesterase is responsible for the rapid clearance of succinylcholine, and hence its short duration of action. Hereditary deficiency of this enzyme (especially when homozygous) can be associated with prolonged paralysis (for many hours). The duration of paralysis may be prolonged to a modest degree in a variety of situations associated with acquired reductions in plasma cholinesterase such as pregnancy, sepsis, burns, renal failure, liver failure, or following plasmapheresis (14,176). Clearance of non-depolarizing NMBA is independent of plasma cholinesterase.

Other untoward effects of succinylcholine include increasing gastric, intraocular, or intracranial pressures (14,84). Although rising gastric pressure might predispose to regurgitant aspiration during intubation, it is said that this effect may be offset by a simultaneous increase in lower esophageal sphincter tone. The drug should not be used for patients with acute glaucoma or with penetrating eye injury. Intracranial pressure increased by 15 to 20 mmHg with no change in blood pressure (and hence a drop in cerebral perfusion pressure) in a series of patients with reduced intracranial compliance (CNS tumors with significant edema and midline shifts). This effect was not seen with vecuronium (120).

Aminosteroidal NMBA include pancuronium, vecuronium, and rocuronium. The onset of action (time to maximal twitch suppression after bolus injection of 1 X ED_{95}) is 2 minutes for pancuronium and 2 to 2.5 minutes for both vecuronium and rocuronium. Pancuronium has the longest duration of action and is therefore used as either intermittent bolus or continuous infusion. Under OR conditions its duration (time to recovery of T4/T1 ratio > 70%, which is usually considered full clinical recovery) is a little over 1½ hours. Under clinical conditions in the ICU the duration of action for these drugs is significantly quite longer, e.g. it may be more like 12 hours for recovery sufficient to support spontaneous movement and breathing with pancuronium (34).



Recovery under OR conditions with both vecuronium and rocuronium is about 30 to 40 minutes. In one comparative trial using ICU patients the median time to 70% train-of-four ratio was actually 1½ hours in 30 patients who had received vecuronium for an average of 2-3 days (133). Thus, pancuronium has the longest duration of action, but all have clinical durations in ICU patients which are considerably longer than when these drugs are used in the OR.

Clearance

Pancuronium elimination is primarily dependent upon renal (40%) and biliary (10%) excretion. The drug is also metabolized by the liver. Its principal metabolite, 3-OH-pancuronium, has paralytic activity equivalent to 50% of the parent compound and is excreted in both urine and bile (119). Vecuronium is cleared primarily via biliary excretion (70%) and by the kidney to a lesser extent (15%); however, its principal metabolite is 3-desacetylvecuronium which has significant paralytic activity (182) and which does rely on renal clearance (1). For these reasons prolonged neuromuscular blockade can occur when using either drug for patients with renal or hepatic failure. The active metabolites are not removed during hemodialysis/ultra-filtration (1,172).

As might be expected, liver dysfunction affects the pharmacodynamics of the aminosteroidal NMBA (55). The onset of the drug is slower owing to an increase in the volume of distribution (12,54). This may also contribute to greater drug and metabolite accumulation, and thus potentially add to delayed elimination and prolonged duration of action. The elimination time for both pancuronium and vecuronium are approximately doubled in the presence of either cirrhosis with portal hypertension (54,104) or extra-hepatic biliary obstruction (2,105); elimination of vecuronium was reported to be 60% longer in patients over the age of 70 years when compared to a group aged 26-48 years (108). Postpartum patients an elimination and recovery time which is almost double that of controls (31). Impaired drug elimination is associated with proportionate prolongation of paralysis.

Atracurium and cisatracurium have non-steroidal chemical structures and have several properties that distinguish them from the aminosteroid NMBA (84). These compounds are degraded through several mechanisms. The primary route is via Hofmann elimination, which is the non-enzymatic breakdown of the bisquartinary structure with loss of a water molecule and formation of a tertiary base and a compound called laudanosine (62,158). This process occurs spontaneously in plasma at physiologic pH and body temperature. Although the process is both pH and temperature dependent, the range of pH encountered in critically ill patients does not meaningfully affect the rate of decay. However, environmental or surgical hypothermia does retard the process and delay elimination. These drugs are also broken down in plasma by nonspecific ester hydrolysis; this is not meaningfully affected by either AC or plasma esterase concentrations. In addition, both drugs are acetylated by the liver. Although metabolism may be affected by liver dysfunction, the presence of two other substantial routes of elimination effectively offsets this problem. None of the breakdown products have paralytic activity. Thus, both of these NMBA can be used for patients with significant liver or kidney dysfunction without affecting the duration of NMB (24,44,60,86,127).

Laudanosine

Although the parent compound does not show significant dependence on renal clearance, laudanosine is eliminated primarily via the kidney and is also metabolized by the liver to some extent. Laudanosine binds to opiod receptors in the brain (92). Although it has very weak analgesic effects, it has been shown to produce generalized seizures at very high doses (10-40 mcg/ml) when given to dogs (67,78). This has led to speculation that accumulation of laudanosine in humans might produce similar effects. In rabbits there are no significant EEG changes with laudanosine concentrations of 1 mcg/ml (162). Atracurium given to cats at doses of 4 X ED95 had no effect on lignocaine-induced seizure threshold (101), suggesting that it might be safe in the face

of a seizure disorder. Unfortunately, this study was conducted with halothane anesthesia; volatile anesthetic agents are protective against seizures with laudanosine (152).

Following a single bolus of 2 X ED_{95} of atracurium in patients with normal renal function undergoing elective surgery, the peak level of laudanosine has been observed to be only 0.2 – 0.3 mcg/ml (59,60). Patients with renal failure had peak levels of 0.8 mcg/ml (59). During long-term infusion of atracurium to patients on mechanical ventilation in the ICU, laudanosine levels have been noted to be higher: 0.4 mcg/ml after 30 - 38 hours of infusion (72,127) and from 1.9 to 5.0 mcg/ml after 2 - 9 days of infusion (183). One patient who received atracurium for 38 days had a final laudanosine level of 0.4 mcg/ml (72). All of these levels are considerably below those required for seizure activity in dogs (10–14 mcg/ml). Thus far there have been no clinical reports of seizure activity associated with long-term atracurium infusion. Though limited to a small number of patients, one study has shown that long-term infusions of atracurium appear to produce similar peak laudanosine levels and are associated with comparable laudanosine clearance rates when comparing patients with and without renal failure (127).

Cisatracurium is one of 10 isomers of atracurium (170). It was developed primarily because it is approximately 5 times more potent than atracurium (ED_{95} 0.05 mg/kg and 0.23 mg/kg for cisatracurium and atracurium, respectively). For this reason, considerably less cisatracurium is required to achieve adequate NMB. Both drugs have similar onset (5 minutes to 100% twitch suppression), duration (40 minutes to 70% twitch recovery), and elimination characteristics at doses of 2 X ED_{95}.

It is not likely that the potential for laudanosine accumulation (from atracurium and cisatracurium) and resulting seizure activity has any clinical relevance in patients.

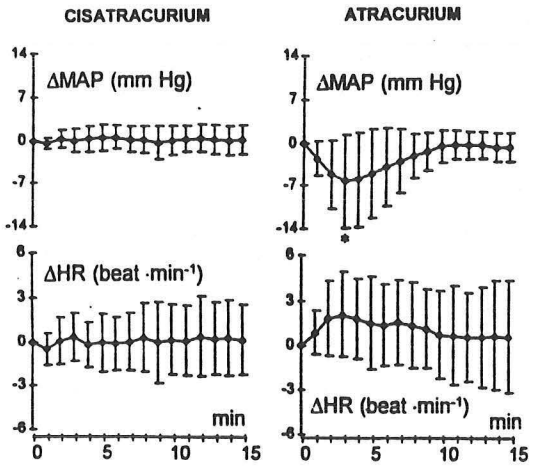
Since the dosing is significantly less with cisatracurium, laudanosine levels are considerably lower after bolus injection (0.016 mcg/ml and 0.021 mcg/ml in patients with and without end-organ failure) (44). Long-term infusion data are not currently available, but the pharmacokinetic data and lower dose requirements for cisatracurium strongly suggest that laudanosine levels will likely always be lower than with atracurium and almost certainly well below (by 1-2 log difference) the levels associated with seizures in animals.

Histamine Release

Of the drugs detailed in this discussion, atracurium is the only one thought to have significant histamine releasing properties (14,84,85,87). Much has been made of the histamine releasing properties of NMBA, largely because it was a significant problem with older agents, especially tubocurarine. Atracurium has approximately one third the histamine-releasing properties of tubocurarine (85). Cisatracurium causes almost no histamine release (46); the same is true for pancuronium. Although there is a case report of vecuronium causing a histaminoid reaction (53), subsequent modern trials have not detected significant histamine responses (46), even in asthmatic patients undergoing elective surgery (30).

NMBA cause histamine release from mast cells through a non-immunologic mechanism which is not cytotoxic, does not require energy, and is calcium-independent; it appears that histamine release is somehow caused by its chemical displacement from mast cell granules (10). As such, its release is not associated with the other mediators and responses which occur with anaphylaxis and/or complement activation. Furthermore, chemical release of histamine by NMBA is confined to serosal mast cells found in loose connective tissue (such as skin). Mucosal mast cells (as in bronchi) are resistant to this effect and appear to respond only to immunologic stimuli. In fact, anaphylactic reactions are especially uncommon with all NMBA. Furthermore, overt bronchospasm

is decidedly uncommon with all of these agents (10,30,46,88,102). Only 0.4% of 477 patients who received atracurium in a post-marketing survey in the U.K. were thought to have developed bronchospasm (102); the incidence was 1.5% of 1013 patients in the U.S. (88). In both of these reports the incidence of these effects was the same with vecuronium. In a study of 30 asthmatic patients who were given atracurium after they had already been intubated and placed on mechanical ventilation in the operating room, there was no measurable increase in peak airway pressure, much less evidence of overt wheezing (30).



The non-immune chemical release of histamine is more often associated with cutaneous flushing, decreased systemic vascular resistance, drop in blood pressure, and increased heart rate. These reactions may actually be fairly common with atracurium. Post-marketing surveys suggest they occur in 1.0 to 2.5% of cases (88,102); however, prospective series suggest that these responses may occur in 60% of cases (30). In fact, the incidence of similar effects with vecuronium (which is generally said to not have histamine-releasing properties) was comparable to atracurium in these studies. Usually the response is very short-lived (minutes), fairly minor physiologically (BP or HR changes of 10-20% from baseline), and very rarely require specific intervention (10,30). Histamine release is potentiated by giving either high doses or very rapid injection. The "threshold" dose for atracurium is 0.5 mg/kg, 2 X ED95, which is associated with a 30% histamine responder rate. The response is minimized by giving the drug more slowly (10) and can be blocked by pre-treating with a combination of H-1 and H-2 histamine blocking drugs (3).

It is not clear that histamine release by modern agents is clinically relevant except perhaps when choosing an agent for emergent airway intubation.

Hemodynamic Effects

Pancuronium produces a consistent tachycardia (10 to 30 beats per minute) through its ability to produce parasympathetic blockade ("vagolytic" effect); blood pressure may rise slightly (14,84); none of the other NMBA in this discussion produce this effect to any significant degree.

Vecuronium has a well established hemodynamic safety profile, showing almost no effect on heart rate, blood pressure, cardiac output, or peripheral vascular resistance at doses up to 3 X ED_{95} (46) and in patients with coronary artery disease (97). Vecuronium and rocuronium have little or no direct cardiac effects. Atracurium may cause transient hypotension and tachycardia as a manifestation of histamine release, but significant hemodynamic alterations are uncommon (65,130). Cisatracurium has no direct cardiac effect (97) even at doses up to 5 X ED_{95}.

While succinylcholine may increase intracranial pressure (see above), vecuronium is well tolerated. Cisatracurium has almost no effect on intracranial pressure or cerebral perfusion pressure, while atracurium may cause cerebral perfusion pressure to fall by 5-6 mmHg for 5-10 minutes as a result the blood pressure fall seen with histamine release (147).

In choosing a NMBA for use during mechanical ventilation the most relevant considerations are clinical duration of action, hemodynamic effects, tachyphylaxis, end-organ dysfunction (especially renal and hepatic), age of the patient, and cost. Pancuronium is considerably less expensive than the other non-depolarizing NMBA. Its inherent long duration of action make it less useful when it is desirable to periodically withhold NMB to assess neurologic status. It should be avoided in patients with baseline tachycardia or ischemia due to its vagolytic properties.

Pancuroium should also be avoided in patients with impaired renal or hepatic function or when it is expected that NMB will be needed for more than 1 to 2 days to prevent accumulation of drug and active metabolites. Because of its very low cost, it is still a good choice for patients who have none of these contraindications. In practical terms, however, the number of patients who meet these criteria who truly need NMB is fairly small (especially in an MICU patient population) and the overall cost savings may not be significant.

Atracurium use has largely been supplanted by cisatracurium. Atracurium has greater propensity for tachyphylaxis and histamine release, transient reduction in cerebral perfusion pressure when intracranial compliance is reduced, and produces higher levels of laudanosine (especially in renal failure). Although these differences may be of marginal clinical importance, recent market developments have resulted in cisatracurium being priced at or below atracurium.

Thus, when an alternative to pancuronium is needed, the choices include vecuronium, rocuronium, and cisatracurium. Vecuronium and rocuronium are very similar in their pharmacologic properties when given as continuous infusion; vecuronium has some advantage to the extent that ICU practitioners have developed considerable experience in its use. Vecuronium and cisatracurium both have little, if any, direct effect on hemodynamics or cerebral perfusion pressure. Vecuronium should be avoided in patients with conditions associated with impaired clearance of the drug or its metabolites (renal and especially hepatic dysfunction). The clinical duration of NMB after prolonged infusion has been reported to be 6 hours with vecuronium and 1 hour with cisatracurium in one comparative ICU trial (133). Vecuronium has a greater propensity for tachyphalaxis (see above). The clearance of vecuronium is also prolonged in patients over the age of 70 years (93,108,125), but this does not appear to be the case with cisatracurium (125). Despite some differences among these agents with regard to histamine release, none seem to have significant effect on overt bronchospasm (see above). Although it was once speculated that the use of non-steroidal NMBA such as cisatracurium might be mitigate the development of prolonged weakness from NMBA/steroid-induced myopathy, current evidence does not support this conclusion. There does not appear to be any clinical or theoretical advantage of one NMBA over another with regard to development of critical illness polyneuropathy in patients with multiple organ dysfunction. Thus, the choice of a NMBA for use in mechanical ventilation is not influenced by the presence of airways obstruction or concomitant use of steroids. Multiple organ dysfunction is only important with regard to drug/metabolite clearance, which influences recovery from NMB, and not the incidence of critical illness neuropathy.

Pancuronium still has a limited role as a first choice for NMB. Cisatracurium is likely the best alternative, especially when its cost is less than either vecuronium or rocuronium.

When the cost of cisatracurium significantly exceeds either of these agents, the first alternative would be the use of either vecuronium or rocuronium; cisatracurium would be used as a third-line agent for patients with significant renal or hepatic impairment (and perhaps for those over the age of 70 years).

Cost Comparisons

Direct cost comparisons between the NMBA given as continuous infusion can be made by converting average infusion doses (mcg/kg/min) taken from the literature (32,76,134) to drug requirements for an average 70 kg patient over 24 hours (mg) and multiplying by the direct cost of the drug ($/mg) to yield a cost per day of treatment (see appendix). Total pharmacy costs are higher, but are comparable between agents when given as continuous infusion. Pancuronium has always been substantially less expensive than other agents. Previous reports have suggested that vecuronium was less costly than either atracurium or cisatracurium (76). However, recent market developments have considerably altered this relationship and there is substantial inter-institutional variation in pricing (retail pricing is fairly irrelevant for these drugs). For example, as of December, 1998 the daily costs for NMBA at the Dallas VA Medical Center are as follows: pancuronium, $12-16 (0.07- 0.1 mcg/kg/min); cisatracurium, $118-136 (2.6- 3.0 mcg/kg/min); rocuronium, $202 (10.0 mcg/kg/min); vecuronium $196-396 (1.5-3.0 mcg/kg/min). In our MICU, we therefore currently prefer cisatracurium when pancuronium is not used.

While episodes of prolonged weakness following use of NMBA may be relatively uncommon, they are by no means rare, especially in the very clinical situations where they are most likely to be employed. The cost of one such episode may be substantial, $66,000 by one estimate (143). Even the prudent selection of NMBA and the use of appropriate monitoring during NMB may not altogether obviate the occurrence of such complications (see below). As such, it is probably not an oversimplification to say that the most cost-effective strategy is to minimize the use of NMBA altogether.

INDICATIONS

Airway Intubation

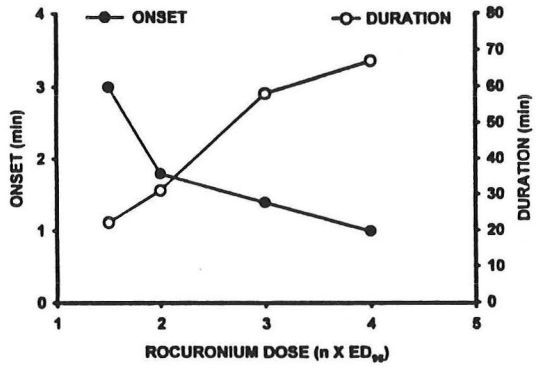
The commonest indication for use of NMBA is to facilitate intubation of the airway. In controlled OR situations and during emergent intubation of non-comatose patients, intubation is always preceded by administration of one or more agents for sedation (benzodiazepines, anesthetics) and/or analgesia (morphine, fentanyl). Used appropriately, these agents allow for uncomplicated intubation in many, if not most, cases (83). In some situations NMBA may be necessary to achieve appropriate relaxation to allow for adequate laryngeal visualization and to prevent unnecessary trauma. However, their use does not guarantee success and by definition eliminates the patient's own protective reflexes and creates overt apnea. NMBA are therefore not a substitute for proper attention to the other aspects of airway management and use of bag-mask ventilation; in fact, they likely heighten the need for their skillful use. Thus, in emergent situations, NMBA should always be used judiciously and not considered routine.

Succinylcholine is the "prototype" for facilitating intubation in the OR. It has a very rapid onset, achieving complete NMB and good to excellent intubation conditions within 60-90 seconds (83). Its short duration of action (5-8 minutes) is also desirable, especially when used for intubation in short-duration surgical procedures. However, as detailed earlier, this drug is associated with a wide variety of potential untoward effects and is contraindicated in many situations. In the setting of elective surgery, pre-anesthesia evaluation allows the physician to identify most (but not all) of these problematic situations so that an alternative agent can be selected. Further, some of the effects produced by the depolarizing action of succinylcholine (such as fasciculations and postoperative muscle pain) can be prevented or minimized by giving a small, non-paralyzing dose

of a non-depolarizing NMBA, e.g. 0.01 mg/kg of vecuronium (14,174). This is sometimes referred to as "precurarization" or the "priming principle". In emergent situations it is not clear what value there is to this approach since in the time involved with sequential precurarization and succinylcholine is longer than would be required using appropriate doses of either vecuronium or rocuronium.

The situation during emergent airway intubation is considerably different from the OR. By definition these patients are more likely to have coexisting acid/base or electrolyte disturbances, increased intracranial pressure, or any of the other conditions for which the drug might be contraindicated; given the urgency of the situation there is often no opportunity to carefully determine these issues. Emergent airway intubation is always followed by use of supportive mechanical ventilation so that the very short duration of succinylcholine is far less relevant; indeed, it may be desirable to allow NMB to persist for 30 to 45 minutes while assessment of respiratory mechanics and ventilator adjustment are accomplished. The short duration does not provide a realistic margin of safety in cases of failed intubation; even 5 to 8 minutes of apnea can produce catastrophic anoxia, especially when circulation is impaired. Indeed, the onset of succinylcholine may be less rapid in critically ill patients due to reduced distribution (low cardiac output) and higher volume of distribution. Thus, succinylcholine may not be the ideal agent for use in emergent situations.

At equipotent doses (1 X ED_{95}) succinylcholine always has the shortest onset when compared to the other non-depolarizing agents. However, the onset of a NMBA is directly proportionate to the dose and rate of administration, so that NMB can be achieved more rapidly with rapid, bolus injection of higher doses. Rocuronium at doses of 2 X ED_{95} (0.6 mg/kg) can produce maximal NMB with good to excellent intubation conditions in 1 to 1 ½ minutes in OR situations (22,83,177) and is comparable to succinylcholine (83). The onset of vecuronium at doses of 2 X ED_{95} (0.1 mg/kg) is comparable to rocuronium (13,22).



However, the duration of NMB may be prolonged at higher doses. The clinical duration of a single bolus of rocuronium or vecuronium at 2 X ED_{95} is 30 to 45 minutes in OR situations. Higher doses produce only marginal shortening of onset time, but do contribute to more prolonged duration. Neither atracurium or cisatracurium can achieve onset times comparable to rocuronium or vecuronium, except at very high doses such as 5 X ED_{95} for cisatracurium. Further, these high doses given rapidly produce significant tachycardia and hypotension with atracurium due to histamine release (see above) and the NMB lasts for over 1 ½ hours with cisatracurium. Thus, the non-steroidal NMBA are not generally used for emergent airway intubation.

Vecuronium (0.1 mg/kg) and rocuronium (0.6 mg/kg), doses of 2 X ED_{95}, are preferred alternatives to succinylcholine for emergent airway intubation.

Rocuronium has been reported to produce an increase in heart rate of 35% above baseline at 2 X ED_{95} (22), though other studies have not demonstrated significant cardiovascular changes or evidence of histamine release (83,107,177). No significant cardiovascular changes have been reported with vecuronium at these doses in OR situations (13,22). Thus, vecuronium may be marginally superior to rocuronium in this regard. Another practical advantage of vecuronium is that it can be stored at room temperature and is thus suitable for placement on cardiac arrest ("crash") carts; succinylcholine, pancuronium, rocuronium, atracurium, and cisatracurium all require refrigeration (package insert data).

Mechanical Ventilation

NMBA are also commonly used to facilitate mechanical ventilation. Their use can be of particular benefit for patients with status asthmaticus or severe ARDS when non-conventional modes of ventilation are required. Asthmatic patients may require NMB to manage high airway pressures and to facilitate permissive hypoventilation when severe air-trapping creates high levels of auto-PEEP with attendant "ventilator tamponade" and hypotension (43). Although inverse ratio ventilation with or without airway pressure-control may improve gas exchange and minimize so-called "baro- or volu-trauma" in patients with severe ARDS, the pattern of ventilation is so contrary to normal pressure/flow relationships that NMB is almost always necessary to suppress inspiratory effort, maintain consistent pressure/flow conditions, and prevent excessive airtrapping, auto-PEEP, and hypotension. Experienced ICU practitioners will attest that in some such situations, sustained NMB is both necessary and potentially lifesaving. However, while these salutary effects of NMBA most commonly occur in these two clinical settings, their use must be weighed against potentially severe complications. Prolonged muscular weakness and attendant prolonged mechanical ventilation (and its complications) may especially occur in conjunction with NMBA and high-dose steroids (asthma) or multiple organ dysfunction (ARDS), as will be detailed below.

In both asthmatics and patients with ARDS, it is clear that the use of NMBA may lead to improved respiratory mechanics and gas exchange. Indeed, use of NMB is an easy "quick fix" for many patient/ventilator interaction problems. However, there is considerable evidence that similar improvements can be achieved with appropriate ventilator adjustment or adequate sedation (41,43,81). Adequate identification and correction of problems which might stimulate inappropriate patient/ventilator coordination ("fighting the ventilator") such as fever, pain, anxiety, inappropriate flow or triggering settings, inappropriate selection of ventilator mode, bronchospasm, retained secretions/mucous plugging, volume overload, cardiac ischemia, sepsis, pulmonary embolism, primary CNS dysfunction, acidosis, etc must all be considered and appropriately addressed before instituting prolonged use of NMBA.

Asthmatics requiring mechanical ventilation, for example, can usually be maintained with sufficient sedation and appropriate ventilator adjustment (41,43). In Darioli's series, 70% of patients with status asthmaticus were successfully managed with controlled hypoventilation using benzodiazapine sedation without NMBA (43).

With appropriate sedation, patients with ARDS can usually be managed with conventional modes of ventilation (tidal volume 10-15 ml/kg, volume-limited modes, peak airway pressures 30-50 mmHg, rate adjusted to normalize CO2); only about 20% of patients managed in this way require NMBA (159). Non-conventional modes such as pressure control/inverse ratio ventilation are generally used for situations where airway pressures are excessive and/or oxygenation cannot be maintained; they are usually employed later in the course of illness.

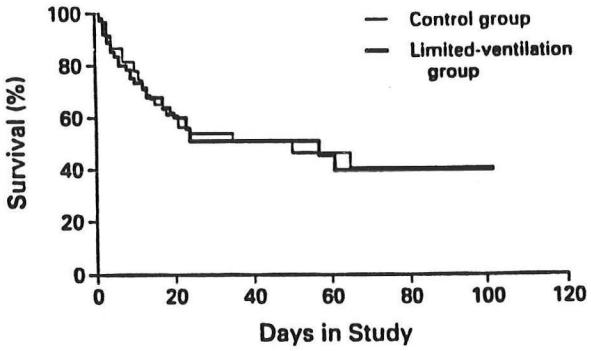
Nonetheless, many patients with ARDS experience barotrauma (pneumothorax, hypotension). It is also thought that cyclic alveolar collapse/re-expansion (sheer) and overdistention (volutrauma) may actually contribute to lung injury. For these reasons, non-conventional ventilatory modes and

strategies have been recommended for all patients with ARDS (some prefer the term "protective" ventilation). These non-conventional approaches involve smaller tidal volumes (5-8 ml/kg), pressure-limited modes, lower peak airway pressures (less than 30 cmH2O or less than 20 cmH2O above PEEP), and permissive hypercapnia.

However, there is now compelling evidence that these non-conventional or "protective" techniques are not inherently beneficial when applied to all patients with early ARDS; these techniques likely are only necessary in those patients with severe lung injury and persistently high airway pressures (82). Amato, et al randomly assigned patients with early ARDS to conventional or protective management strategies. They found a lower rate of barotrauma and lower 28-day mortality in the protective group. However, mortality at discharge was not statistically different and there was excess early mortality (first several days) in the control group which would not be explained by the theoretical basis for "protective" ventilation (7). On the other hand, Weg, et al found no correlation between barotrauma or mortality with respect to either airway pressure or tidal volume in a group of ARDS patients treated with conventional ventilation (175). Stewart, et al also randomly assigned patients with early ARDS to conventional and protective management and found similar rates of barotrauma, multiple organ failure, and mortality in the two groups (159). One clear difference between these two ventilation strategies is the need for NMBA. Stewart, et al found that the need for NMBA was 75% greater with the nonconventional, protective strategy (159). It is worth noting that in that same study 60% of patients were successfully managed with the protective strategy using adequate sedation without NMBA.

	Limited Ventilation	Conventional Ventilation
NMBA Used (%)	38	22 *
Ventilator Days	16.6	9.7
ICU L.O.S. (days)	19.9	13.7
Hospital L.O.S. (days)	33.7	27.4

Stewart, et al, 1998



In these clinical situations NMB is used to facilitate mechanical ventilation by effectively ablating the need for patient/ventilator interaction. It has been suggested that NMBA are beneficial in that they are associated with reduced total respiratory resistance, work of spontaneous breathing, and reduced oxygen consumption requirements (38,87,106). NMB does not directly affect airway smooth muscle tone or lung compliance. Total pulmonary resistance is reduced by relaxing the respiratory muscles, thereby diminishing the elastic load imposed by the chest wall and abdomen. Work of breathing is reduced both through diminished elastic load as well as by reducing overall minute volume. Reducing oxygen consumption might further reduce ventilation requirements and improve gas exchange by reducing peripheral oxygen extraction, reducing venous admixture and improving arterial saturation in situations where there is marked intrapulmonary shunting, such as ARDS.

There is little question that many of these effects can be achieved with NMB in patients who have excessive and inappropriate respiratory drive and resulting hyperventilation, who are actively "fighting the ventilator, or showing marked distortions of the inspiratory pressure waveform. However, the use of NMB does not diminish the need for continued sedation and there is little evidence that NMB has any advantage over adequate sedation/analgesia and appropriate ventilator management in this regard. Oxygen consumption and/or work of breathing can be

reduced during mechanical ventilation with sedation/analgesia (36,138) or through ventilator adjustment (67,114). In fact, if patients are first adequately sedated, paralysis does not independently or incrementally alter work of breathing or total respiratory compliance (115), oxygen consumption (126), or mixed venous saturation (36). Furthermore, there is evidence that total elimination of diaphragm activation may potentially worsen gas exchange via increased ventilation to non-dependent lung zones (135).

The primary role of NMBA for patients receiving mechanical ventilation is to facilitate patient/ventilator interaction, but NMBA should be used only after appropriate correction of other contributing clinical factors and achievement of maximal sedation have failed.

Paralytics have also been suggested for use as a "chemical restraint" for combative patients, but similar arguments pertain with respect to the preferential use of adequate sedation and analgesia. The result of disconnection from the ventilator or loss of airway during procedures and patient positioning can be catastrophic when the patient's protective reflexes and ability to breath spontaneously have been ablated. Other uncommon indications for NMBA include the management of patients with tetanus (57,132,167) or to minimize the substantial oxygen consumption associated with shivering during rewarming after surgical or environmental hypothermia (136).

COMPLICATIONS

Use of NMB is associated with several general complications such as corneal abrasion, pressure ulceration, thromboembolism, and deconditioning. Appropriate eye precautions, knee/heel protection, and DVT prophylaxis should be employed. Passive exercise has no benefit in terms of preventing deconditioning when the patient is paralyzed. Appropriate use of concomitant sedation/analgesia is necessary to prevent "awake paralysis" which can be a terrifying experience for the patient (128) and which can be a cause for increased heart rate or blood pressure.

The most significant complications associated with non-depolarizing NMBA used in the ICU relate to the occurrence of prolonged weakness, which may substantially prolong the duration of mechanical ventilation and its attendant complications, prolong ICU and hospital length of stay, and require additional costs for diagnosis and rehabilitation. As noted earlier, prolonged weakness occurs in about 5% of ventilated patients following NMBA (122), in as many as 40-45% of asthmatics treated with steroids and NMBA (50,151), and between 30-70% of patients with ARDS and multiple organ dysfunction who require NMBA (17,148,180).

In general, prolonged weakness following NMBA occurs either from prolonged neuromuscular blockade (pharmacokinetic effects) or from actual damage to peripheral nerve and/or muscle (pathologic effects). These pathologic effects tend to cluster in two clinical syndromes: an acute myopathy seen in patients (usually asthmatics) treated with both steroids and NMBA and a motor polyneuropathy seen in the setting of severe critical illness, especially ARDS with multiple organ dysfunction. These syndromes are characterized by severe peripheral weakness (often quadriparesis), prolonged ventilator dependence (weeks), and slow recovery (weeks to months). The weakness persists long after the pharmacologic effects of the NMBA have resolved and so there is no evidence of persistent NMB as assessed by electrostimulation ("train-of-four", TOF) monitoring.

Prolonged Neuromuscular Blockade

Many of the earlier reports of post-paralytic weakness were most likely due to prolonged neuromuscular blockade (11,129,140,141,148). This is recognized when flaccid paralysis or

weakness persists after cessation of NMBA. It is confirmed by persistence of a depressed response to electrical stimulation (TOF 0/4 or 1/4, see below). Prolonged NMB results from pharmacokinetic effects of NMBA. It is therefore more likely to occur with drugs with long clinical duration of action, such as pancuronium; when excessive doses are given; when there is impaired clearance, e.g. impaired hepatic or renal function, age over 70, postpartum patient, etc; or when there are drug interactions (see above).

In these patients the prolonged NMB generally lasts for a period of 6-18 hours following cessation of the drug, though weakness may last for several days (especially with pancuronium). Although there have been reports which have implicated prolonged NMB of weeks in duration, there are features in these reports that suggest the presence of either myopathy or polyneuropathy as better explanations for the prolonged weakness (69,122,129). Most of these effects can be minimized through appropriate selection of a NMBA in individual cases, as was discussed in detail earlier. Excessive dosing can be minimized through the use of clinical and/or electrical TOF monitoring (see below).

Steroid Myopathy

There were early case reports (89,100,110) followed by a "cluster" of seven patients over 18 months in one institution (68) describing a severe acute myopathy occurring in asthmatics who received pancuronium. Reports followed which demonstrated that this disorder is common with other steroidal NMBA such as vecuronium (42,71,79,96,98,113,135,151). Although there was early speculation that the mechanism of this myopathy was somehow related to the steroid-like structure of pancuronium and vecuronium, this is clearly not the case. There are now numerous reports of the same disorder with non-steroidal agents such as atracurium (27,80,103,112,117,166). In one series, the frequency of the myopathy was the same in patients receiving steroids and either vecuronium or atracurium (103). The disorder is not uncommon; it may occur in as many as 40-45% of patients who receive steroids and NMBA (50,151), especially when NMBA exceeds 24 hours (98,103).

There have now been over 60 cases reported in the literature which describe an acute myopathy which shares similar features. It is occurs in patients receiving concomitant high-dose steroids (the equivalent of 40 mg every 6 hr or more of hydrocortisone) and NMBA. The vast majority of patients are being treated for asthma, though there is at least one report in a transplant recipient (161). All have received NMBA while on mechanical ventilation, usually for more than 24 hours. The patient usually is identified in the context of difficulty weaning from the ventilator after discontinuing NMBA. Electrical TOF monitoring shows no residual NMB.

There is profound weakness, often described as flaccid quadriplegia, with marked muscle atrophy. Deep tendon reflexes are diminished with normal plantar responses. There is generalized involvement of all four limbs, including both proximal and distal muscle groups. CNS function is not affected and cranial nerve dysfunction does not occur, though involvement of ocular muscles has been described in rare cases (153). In addition to the muscle atrophy, there is pathologic evidence of muscle necrosis which is associated with elevated creatine kinase (CK) levels in many cases. The CK often exceeds 1,000 U/L and may occur in as many as 76% of cases (50). However, CK elevation is not particularly sensitive as overall only about 40-60% of cases will have abnormal CK when it is checked; the CK elevation may be missed, especially if not measured within the first day or so of treatment. Though not specific, the presence of an elevated CK helps to distinguish this from other entities, especially critical illness polyneuropathy (see below).

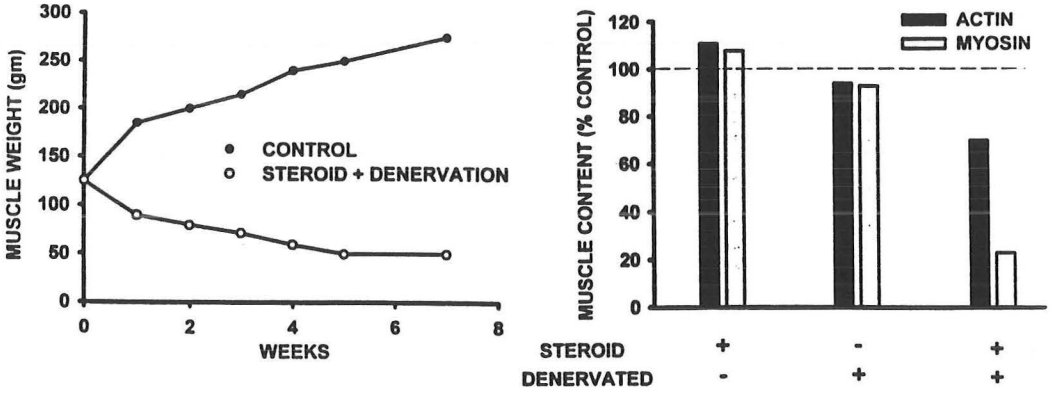
Muscle biopsy typically shows diffuse necrosis, with selective loss of myosin on histochemical staining, and little or no inflammation (8,42,68,71,79,89,100); this constellation of findings is not common in other myopathic disorders. Electrophysiology studies done in these patients are

somewhat variable, especially when done late in the patient's course. In general, they show no evidence of neuropathy (normal nerve conduction velocities, latency, and nerve compound action potentials) or impaired neuromuscular transmission (lack of diminution with repetitive stimulation). Electromyography is typically said to have a myopathic pattern with low amplitude muscle compound action potentials of short duration along with fibrillation potentials, positive sharp waves, or increased activity with spontaneous movement. Recovery is the rule in patients who survive the acute illness, but may require many weeks or months of rehabilitation.

The classic form of steroid myopathy described by Cushing is far more common, but it is slowly progressive, almost always has normal CK levels, and proximal weakness predominates (71). An acute myopathy has been described in patients who have received very high doses of corticosteroid (1-2 grams/day of hydrocortisone) who did not receive NMBA (96,171,179). However, these reports are extraordinarily rare compared to the overall experience with steroids in general and especially in relation to the frequency with which myopathy is seen in those who have received NMBA. Animal studies of high-dose corticosteroids show some similarities with non-inflammatory fiber necrosis; this is particularly notable in the diaphragm and other muscles of respiration, at least in rabbits (40,61). As noted earlier there was early speculation that NMBA might be involved in this myopathy because of their steroid-like structure. However, there is no evidence of actual binding of NMBA to muscle steroid receptors, the drugs do not have clinical corticosteroid effects (137), and the syndrome is seen with equal frequency in patients receiving non-steroidal NMBA (see above). There are no reports of this type of myopathy in patients who have received NMBA without concomitant steroids.

Disuse atrophy has also been implicated in this syndrome (99). Although immobilization can produce atrophy and an increase in cytosol steroid receptors in animal models (51,90), morphologic lesions are different (90), and the quantitative muscle loss is considerably less. Thus, the pathophysiologic mechanism of this syndrome likely involves synergism between the paralytic effect of NMBA and corticosteroids.

Development of acute myopathy with NMBA and steroids is likely due to chemical denervation and is <u>not</u> restricted to steroidal NMBA.



This is supported by work in animal models. Denervated skeletal muscle from rats treated with dexamethasone develops marked atrophy of type IIB fibers, with thick myofillament depletion. Myosin content is markedly reduced as compared to actin. The muscle's loss of tension generation is disproportionate to the loss of muscle mass. The effects are minimal in the muscles of animals

which have only been denervated or from those receiving steroid alone; the combination producing marked atrophy and myosin depletion (139). Similar studies have shown that this effect is associated with up-regulation of cytosol corticosteroid receptors (52) and is reversible following reinervation (116). The findings in these animal studies are remarkably similar to those in asthmatics receiving NMBA and steroids, suggesting that NMBA act by chemically denervating the muscle, up-regulating muscle steroid receptors, thus increasing susceptibility to acute corticosteroid myopathy.

Critical Illness Polyneuropathy

In the early 1980's Bolton et al described a group of patients from a single Canadian ICU who developed a severe polyneuropathy in the setting of sepsis and multiple organ dysfunction (20). This and several subsequent reports from the same institution form the basis for a syndrome they termed critical illness polyneuropathy (17,18,21,180,185). They have suggested that as many as 70% of patients who have been septic for over two weeks will have electrophysiologic evidence of polyneuropathy, but overt weakness which is clinically apparent is seen in 50% of those with prolonged courses. Similar findings have been reported from other institutions, though not with the frequency that the Canadian group seemed to observe the phenomenon (123,157,178).

Although this syndrome is often discussed in the context of NMBA, it is not clear that NMBA have any significant role in the pathogenesis of this disorder. Of the approximately 40 patients described by the Canadian group, the exact frequency of NMBA use cannot be determined. It was not stated specifically whether patients received NMBA in the first reports involving approximately 25 patients (20,185); in one report of 15 patients with severe weakness and another 15 with electrophysiologic evidence of polyneuropathy it was stated that "muscle relaxant drugs were rarely used" (180). Two other patients described in case reports apparently did not receive NMBA (157,178). Although a report from the Netherlands of 22 patients with prolonged weakness suggested that this was due to critical illness polyneuropathy and that all but 2 received NMBA, the patients they describe are a mixed lot and likely represent acute myopathy and/or prolonged NMB in the main (123).

As described by Bolton, patients with critical illness polyneuropathy (CIP) present in a manner which is clinically similar to what was described above for the acute myopathy associated with NMBA and steroids. Other than the different settings in which they are described (septic patients with multiple organ dysfunction and asthmatics receiving NMBA and steroids), the clinical differences are somewhat unreliable. Patients with CIP typically do not have CK elevations; though not present in all cases, the presence an increased CK should suggest myopathy. Furthermore, most patients with myopathy have intact sensation, whereas the sensory exam may be (but is not always) abnormal in CIP patients. As with the acute myopathy, recovery is the rule for CIP for those who survive, but recovery often requires weeks to months of rehabilitation.

Electrophysiologic studies are said to fairly characteristic (at least for the Canadian group). There is evidence of primary axonal degeneration, without evidence of demyelination (normal nerve conduction times, latencies), muscle denervation, and no (or minimal) evidence of primary myopathy or of neuromuscular conduction impairment (17,18,20,21,185). Histologic studies, when done have shown axonal degeneration of nerve and denervation atrophy (without overt necrosis).

Peripheral nerve is remarkably resistant to hypoxia per se (56), however nerve blood flow and oxygen delivery is potentially threatened during combined hypotension and hypoxemia (109). Sepsis is also associated with mediators which may produce endoneural edema, increasing endoneural fluid pressure and further impeding the microcirulation (131). It is not clear that NMBA would have any role in this process as they have limited presynaptic effect. Bolton has suggested that increased permeability might allow NMBA to gain access to nerve (19), however, there is no evidence that they are directly toxic.

This, taken in conjunction with the lack of a strong clinical association of CIP and NMBA, suggests that it is unlikely that these agents play a direct role in the pathophysiology of CIP. In fact, the clinical weakness seen in these patients is not entirely due to the neuropathy per se, since there is a disproportionate degree of muscle atrophy. This is not entirely unexpected, since interleukin-1 and other circulating peptides are known to cause muscle degradation during sepsis (9,33).

Critical illness polyneuropathy (CIP) is likely a manifestation of multiple organ dysfunction in the setting of the systemic inflammatory response and/or sepsis.

MONITORING

Virtually all recent reviews and practice guidelines relating to the use of NMBA in the ICU have recommended that patients be monitored during therapy using "train-of-four" (TOF) electrical nerve stimulation (38,75,87,149) along with clinical assessment. This can be done with inexpensive and readily available bedside nerve stimulating units which have been designed for clinical monitoring. The premise is that such monitoring will help to minimize complications by preventing excessive drug administration.

Despite these recommendations, several large surveys have shown that TOF monitoring is not used by the majority of ICU practitioners. TOF monitoring was used routinely by 34% of anesthesia intensivists (95) , 41% of ICU nurses (94), and by only 21% of ICUs with formal pulmonary/critical care training programs (76). Some have interpreted this as evidence that we still need to "get the word out." It is more likely, however, that the majority of practitioners have recognized the practical difficulties involved with TOF monitoring and have come to appreciate that these recommendations are largely based upon habit, dogma, and limited data.

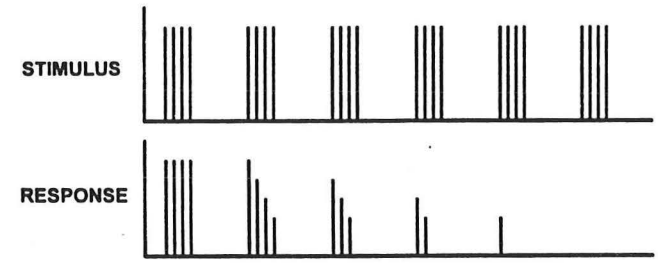
Clinical use of neural stimulation for monitoring NMB developed in the OR to allow anesthesiologists to be able to quantitatively assess the degree of NMB, especially during recovery. The techniques which evolved in this setting are largely based upon a desire to be able to know that total paralysis was being maintained during surgery and more importantly, to be able to know when the clinical effects of NMB had resolved during recovery. A variety of techniques exist, including various permutations of equipment complexity, stimulus pattern/intensity, response observation, and desired endpoints.

All techniques involve delivering an electrical impulse to a nerve via transcutaneous electrodes. Stimuli may be delivered as a series of single twitches, as a tetanic contraction, as a series of single twitches following a tetanic contraction, or by periodically delivering trains of twitches. These various stimulus patterns are discussed in detail in several articles by Ali (4-6). For a variety of reasons, most clinical applications have adopted the use of trains of four stimuli of 0.2 msec duration every 0.5 sec (2 Hz); the TOF are repeated every 12 sec. Bedside clinical units are generally preset to deliver this stimulus pattern (with minor variations). The electrical output (stimulus voltage) can be adjusted with these units, and it is usually recommended that supramaximal voltage is desirable.

NMB is assessed by observing the muscle response to stimulation. In clinical practice this usually involves assessing the response of the adductor pollicis when stimulating the ulnar nerve in the forearm or by assessing the orbicularis oculi after stimulating the facial nerve. The response may be assessed quantitatively either by measuring the muscle's electrical response (EMG) or mechanically by measuring force generation (e.g. strain gauge attached to thumb). Direct

quantitative assessment is largely constrained to OR settings. Muscle response can also be measured semi-quantitatively by visual or tactile observation of muscle contraction.

With the onset of non-depolarizing NMB , there is first a diminution of the magnitude of the evoked response (electrical or mechanical) of successive stimuli in each train, with the last stimulus being affected to a greater degree than the first (so called "fade"). As NMB progresses the later stimuli produce no response at all, until full paralysis is achieved when no response is evoked with any of the four stimuli. During recovery, there will first be evidence of a response only to the first stimuli (TOF = 1/4), then to the first two (TOF = 2/4), and so on. With a TOF = 4/4 (i.e. evidence of some response to all four stimuli), there is a period of further recovery where the quantitative response of the first burst (T1) is greater than the last (T4). When quantitative techniques are used to measure evoked response, the ratio of the height of fourth to the first burst (T4/T1 ratio) is used as an index of recovery. Visual and tactile techniques only allow one to count the number of responses; therefore the T4/T1 ratio is usually used only in OR settings and only applies when TOF = 4/4.



TOF	4/4	4/4	3/4	2/4	1/4	0/4
T4/T1	1.00	0.40	0.00	n/a	n/a	n/a
% PARALYSIS	0	25	50	75	90	100

It is generally held that complete clinical recovery from surgical NMB (0% paralysis) is present with a TOF = 4/4 and a T4/T1 ratio of >0.70 (26,58). It is estimated that there is 50% paralysis at TOF = 3/4, 75% at TOF =2/4, 90% at TOF = 3/4 100% paralysis is achieved at TOF = 0/4 (94). Thus, while there is a quantitative relationship between TOF and degree of paralysis, it is important to note that the relationship is non-linear, that considerable paralysis is present at all TOF levels, and that a TOF = 4 does not guarantee complete recovery (there may be as much as 50% paralysis).

Most recommendations on TOF monitoring suggest that dosing should be adjusted to maintain a TOF = either 1/4 or 2/4. It is implied that 0/4 represents excessive paralysis and that TOF = ¾ or 4/4 is not sufficient to meet clinical endpoints. However, there are no data to support these arbitrary goals, especially in ICU patients. Indeed, there is considerable evidence that the correlation between TOF and clinical assessment of endpoints is quite poor (29,160,169,173).

The usual goal of NMB in the ICU is to facilitate patient/ventilator coordination. The use of TOF = 1 or 2/4 as a goal for this purpose is rather suspect for several reasons. The effect of NMBA on various muscle groups can be quite variable, with the respiratory muscles (larynx and diaphragm) being more resistant than peripheral skeletal muscle (25,48,49); it may take 1.5 to 2 times as much NMBA to paralyze the diaphragm as compared to the adductor pollicis (173). The adductor pollicis is more sensitive than the orbicularis oculi. Thus, measuring the response of one group (e.g. the thumb) may not truly characterize the behavior of another more relevant one (e.g. the diaphragm). As a general rule the response of the orbicularis oculi correlates better with the diaphragm while the adductor pollicis is a better indicator of abdominal muscle status (48,173).

These observations suggest that a different level of NMB may be needed for intubation (laryngeal relaxation), to prevent forced expiratory effort and cough (abdominal paralysis), or for total ablation of inspiratory effort (diaphragm paralysis). Further, it is not clear that total paralysis of peripheral muscle and/or the diaphragm is either necessary or desirable if the goal is to facilitate mechanical ventilation (see above). And finally, it is also not clear what role the level of sedation/analgesia has on the degree of NMB required to achieve a particular clinical goal. Therefore, the ideal target for NMB has yet to be defined with respect to TOF monitoring.

Though proponents of TOF monitoring suggest that it is simple to apply at the bedside pitfalls abound. Electrode placement must be over the nerve; if it is placed near or over the muscle then direct stimulation occurs. This would lead to overdosing since muscle contraction would continue to be observed even in the presence of total NMB; this problem is especially common with facial applications. Lead reversal, poor electrode contact, low battery power, insufficient voltage settings, skin condition and temperature, tissue edema, interference with/from arterial and venous catheters, hypothermia, coexisting peripheral neuropathy, and hypothyroidism can all adversely affect TOF monitoring (29,77,118,124,142,169,173). Reliance on visual assessment and inconsistencies in technique in conjunction with these technical problems gives rise to substantial inter-observer variation. In the typical ICU setting TOF monitoring is done by staff nurses and thus there are often many different observers with varying levels of training and skill.

One study demonstrated that prolonged NMB (defined as a recovery time > 12 hours) was reduced when a standardized approach to NMB monitoring was introduced in a surgical ICU (66). However, this was not a randomized trial and it is not clear what the specific role of TOF monitoring was as opposed to the effects of education and focused attention to clinical monitoring. Further, there was no report of any effect on other outcome measures. Another study by Strange, et al randomized patients to TOF or best clinical assessment after the clinical staff had received intensive education on the use of NMBA; there was no difference in recovery time (160).

	Clinical Dosing (n=34)	TOF Dosing (n=42)
Total drug used (mg)	286	137 *
Neuromuscular recovery (hrs)	3.5	1.7 *
Time to spontaneous breathing (hrs)	2.0	4.8 *

Rudis, et al, 1997

	Clinical Dosing (n=20)	TOF Dosing (n=16)
Total drug used (gm)	9.2	10.5
Neuromuscular recovery (min)	45	50
Mortality	10	4

Strange, et al, 1997

In a recent randomized trial by Rudis, et al, NMB dosing was adjusted either on the basis of TOF monitoring (performed exclusively by the investigators and not the clinical staff) or clinical assessment by the medical team (without TOF). It was observed that less drug was used when titrated to TOF, the average recovery time was shorter with TOF adjustment; median recovery (by TOF criteria) 1.7 vs. 3.5 hours, time to spontaneous breathing 2.0 vs. 4.8 hours. There was no effect on mortality, no significant effect on incidence of prolonged NMB (generously defined as > 4 hours), and no data provided on ICU length of stay (144). Although the authors calculated that TOF monitoring could save $738 per patient based on the data from that study, this savings is based entirely upon the assumption that the average difference in recovery time would be directly translated into an equivalent reduction in ICU length of stay (184). It seems highly unlikely that reducing recovery time by several hours would have a significant effect in this regard.

Others have recommended that it might be useful to incorporate periodic "drug holidays" into ICU protocols to determine the patient's ongoing need for NMB as well as to determine the true minimum dose required for clinical endpoints (150). This concept deserves further attention. It is also important to recognize that in large trials in which NMBA have been used to treat asthmatics or patients with ARDS, the use of TOF monitoring does not prevent the development of the myopathic or neuropathic syndomes of prolonged paralysis. Proper choice of NMBA and careful monitoring (in some fashion) may allow us to minimize the incidence of prolonged NMB (an effect usually measured in hours). However, the use of monitoring techniques (including TOF) should not give us the false sense that we are somehow protecting our patients from serious complications.

While monitoring during NMB seems prudent, many questions remain with respect to best approach (clinical assessment or TOF), goals, technical methods, and clinical impact.

The use of NMBA can be likened to the use of deadly force. Indigenous people of the Americas used NMBA to achieve specific goals (defense, provision of food) and their preparation and use were closely guarded by tribal leaders. Deadly force is used in military applications primarily to achieve specific strategic/tactical goals; the consequences (such as death of combatants or civilians, loss of property) are highly considered, but are secondary to the primary objective. In civilian (police) practice, deadly force is to be used to achieve specific goals as well (apprehension), but the primary goal is always safety (of civilians, officers, and suspects). In both military and civilian applications, the choice of weapon is given considerable attention and their use is restricted to those with appropriate training and experience. NMBA use in the ICU shares many of these qualities: carefully considered choice of agents; restriction to individuals with appropriate knowledge and training; clear definition of goals; and careful, highly selected application.

NMBA, like deadly force, should be used judiciously and with extreme restraint.

Appendix: Comparison of Neuromuscular Blocking Agents

	Succinylcholine	Pancuronium	Vecuronium	Rocuronium	Atracurium	Cisatracurium
Trade name		Pavulon	Norcuron	Zemuron	Triacium	Nimbex
Depolarizing	+	-	-	-	-	-
Duration	short	long	interm	interm	interm	interm
Steroidal structure	-	+	+	+	-	-
ED_{95} (mg/kg)	1.00	0.05	0.05	0.30	0.23	0.05
Intubation						
Dose (n x ED_{95})	1.5	2	2	2	2	3
Dose (mg/kg)	1.5	0.1	0.1	0.6	0.5	0.15
Dose (for 70 kg patient)	100	7	7	40	35	10
Onset (min)[1]	1	4	2.5	2	4	3.5
Duration (duration)[2]	5	100	40	30	60	75
Infusion						
Initial rate (mcg/kg/min)	n/a	0.03	1	5	5	1
Mean rate (mcg/kg/min)	n/a	.07-.10	1.5-3.0	10	10	2.6-3.0
Max rate (mcg/kg/min)	n/a	0.1	3	16	30	10
Duration (min)[3]	n/a	720	60-180	60	60	60
Tachyphylaxis	-	+	++	+	++	+
Active metabolites	-	++	+	+	-	-
Renal clearance	-	++	+	+	-[5]	-[5]
Hepatic clearance	-	+	++	++	-	-
Removed by dialysis	-	-	-	-	n/a	n/a
Laudanosine production	-	-	-	-	+++	+
Hoffman elimination	-	-	-	-	+	+
Histamine release	-	-	-	+/-	+	-
Heart rate	↓	↑	-	↑[4]	↑	-
Blood pressure	↓	↑	-	↓[4]	↓	-
Pulm vasc resistance	-	-	-	↑	-	-
Cerebral perfusion pressure	↓	↑	-	↓[4]	↓	-
Compatible D5W/NS/D5NS	+	+	+	+	+	+
Compatible LR	+	+	+	+	-	-
Refrigerate	+	+	-	+	+	+

[1] time to maximum blockade
[2] time to T4/T1 > 70%
[3] time to T4/T1 > 70%
[4] with rapid bolus
[5] laudanosine relies on renal clearance

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