Selection and Monitoring of Muscle Relaxants During Mechanical Ventilation

Karen F. Shalansky and Stephen J. Shalansky

ABSTRACT

Traditionally, intensive care patients on mechanical ventilation who require muscle relaxant therapy have been treated with bolus doses of pancuronium, a non-depolarizing neuromuscular blocker. Although this drug produces effective paralysis, its use is limited by adverse effects including accumulation with prolonged use, dosage adjustment requirements in the elderly and those with renal or hepatic failure, and cardiovascular toxicity. Vecuronium and atracurium are two newer non-depolarizing muscle relaxants which can be administered by continuous infusion. These agents are more expensive than pancuronium, however, they offer several advantages for critically ill patients requiring continuous paralysis. There is less potential for accumulation, even in patients with renal dysfunction, allowing rapid reversal of paralysis upon discontinuation. In addition, both agents have a higher cardiovascular safety margin. Finally, infusions provide continuous, titratable paralysis as opposed to bolus doses which are re-administered only after signs of recovery. While many patients do not need to be continually paralysed and are well maintained on as required pancuronium bolus doses, atracurium and vecuronium are advantageous in the severely agitated, ventilator-dependent patient. For any patient receiving neuromuscular blocking agents, appropriate monitoring should minimize adverse effects and limit the potential for prolonged recovery.

Key Words: *atracurium, neuromuscular blocking agents, pancuronium, vecuronium, ventilation*

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RÉSUMÉ

Habituellement, les patients des soins intensifs sur respirateur qui ont besoin d'un traitement myorelaxant reçoivent des doses intermittentes de pancuronium, agent bloquant neuromusculaire non dépolarisant. Bien que ce médicament produise une paralysie efficace, son emploi est limité par des effets secondaires, tels que son accumulation lors d'un usage prolongé, par la nécessité d'ajuster la posologie chez les personnes âgées ou souffrant d'insuffisance rénale ou hépatique, et par sa toxicité cardiovasculaire. Le vécuronium et l'atracurium sont deux relaxants musculaires non dépolarisants plus récents administrés par perfusion continue. Ces agents coûtent plus cher que le pancuronium, mais offrent plusieurs avantages au patient dont l'état exige une paralysie continue. Le risque d'accumulation étant moindre, même chez le patient présentant une insuffisance rénale, le renversement de la paralysie est rapide lorsqu'on interrompt le traitement. De plus, ces deux médicaments offrent une plus grande marge de sécurité au niveau cardiovasculaire. Finalement, la perfusion induit une paralysie continue titrable contrairement aux doses intermittentes qui ne sont réadministrée qu'à l'apparition de signes de récupération. Bien que bon nombre de patients n'aient pas besoin d'une paralysie continue et chez qui l'administration de doses intermittentes de pancuronium est suffisante, l'atracurium et le vécuronium présentent des avantages chez le patient très agité sur respirateur. Dans tous les cas, les patients recevant des agents bloquants neuromusculaires doivent faire l'objet d'une surveillance adéquate afin de minimiser les effets secondaires et diminuer le risque de récupération prolongée.

Mots clés: *atracurium, agents bloquants neuromusculaires, pancuronium, respirateur, vécuronium*

Karen F. Shalansky, Pharm.D. (formerly Karen Landsberg) is a Clinical Pharmacy Specialist at Vancouver General Hospital, Pharmacy Services, 855 West 12th Avenue, Vancouver, British Columbia, V5Z 1M9. Tel: (604) 875-4077; Fax: (604) 875-4712.
Stephen J. Shalansky, Pharm.D., is a Clinical Pharmacy Specialist at Lions Gate Hospital, North Vancouver, British Columbia.

INTRODUCTION

Narcotic analgesics and benzodiazepines are commonly used in the mechanically ventilated patient to provide analgesia and sedation. Despite this therapy, some patients remain excessively agitated and continue to resist ventilation, resulting in inadequate gas exchange[1]. In such situations, neuromuscular blocking agents (NMB) can be employed to induce paralysis[2]. Pharmacologic paralysis is also used to improve pulmonary compliance and oxygenation in patients with pulmonary diseases such as adult respiratory distress syndrome[3] and status asthmaticus[4], to reduce excess metabolic demands in the shivering hypothermic patient, to treat tetanus, and to help control elevated intracranial pressure[5]. Muscle relaxants do not provide sedation or analgesia;

the patient is fully alert and able to feel pain. Complete paralysis can be an unpleasant and frightening experience[6], thus, narcotics and benzodiazepines must be routinely administered throughout NMB use.[7] Dosing of sedatives and analgesics during paralysis is difficult, and careful monitoring of blood pressure and heart rate are often the only parameters which can be used to determine their dosing frequency. Caution must also be exercised due to adverse effects associated with muscle paralysis including pulmonary embolism secondary to stasis, and suppression of cough reflex necessitating frequent suctioning.

The ideal agent for paralysis of the mechanically ventilated patient should produce an early, titratable paralysis with a minimum of side effects. It should have a short duration of action and lack cumulative properties to allow rapid recovery from paralysis for neurological assessment and weaning from the ventilator.[8] In addition, elimination should not rely on kidney or liver function which are often compromised in the critically ill. Finally, this agent should be available at a cost which is not prohibitive.

Comparison of Non-Depolarizing Muscle Relaxants

Non-depolarizing agents inhibit the effects of acetylcholine by competitively blocking cholinergic receptor sites at the neuromuscular junction, resulting in paralysis of skeletal (voluntary) muscles.[9] Tubocurarine was the first agent used routinely for paralysis, however, hypotension and bronchospasm resulting from histamine release limited its use.[10] Further research lead to the development of pancuronium which lacks histamine releasing properties.[11] Although pancuronium has become a commonly used neuromuscular blocking agent and is effective for the majority of patients requiring intermittent paralysis, its pharmacology is considered less than ideal for prolonged use in the critically ill patient.

The onset and duration of action of pancuronium are dose-dependent, averaging 3-5 minutes and 40-60 minutes, respectively.[7] It exhibits cumulative properties as illustrated in a study by Fahey *et al* where repeat doses (0.02 mg/kg) resulted in 139% increase in duration of action after the fourth dose as compared to the first dose (160 minutes versus 64 minutes, respectively).[12] Pancuronium is 75-80% eliminated unchanged via the kidneys and 20-25% metabolized, resulting in an increased duration of activity in patients with renal or hepatic impairment, and decreased dosage requirements in the elderly.[11,12,13,14,15] The clearance of pancuronium in children is similar to that described in adults.[16] Although histamine release is minimal, pancuronium possesses vagolytic and sympathomimetic properties leading to increased heart rate, cardiac output, and rarely, supraventricular tachycardia.[11]

Two newer non-depolarizing muscle relaxants, atracurium and vecuronium (a congener of pancuronium), are unique in that they are relatively short-acting, and their clearance is not affected by changes in renal function (Table I). Accumulation is minimal with repeat doses of vecuronium and atracurium producing only a 39% and 5% increase in duration of action, respectively.[12] Both agents also have a high cardiovascular safety margin.[10] Vecuronium does not cause histamine release, whereas atracurium can cause histamine release at doses three times those required to produce clinical muscle relaxation.[11] Based on equivalent doses, vecuronium is approximately double the cost of pancuronium, but one-half the cost of atracurium[17] (Table I).

Vecuronium is eliminated via hepatic metabolism and biliary excretion with a main metabolite only 2% as potent as the parent compound.[11] Severe liver disease and advanced age may prolong the duration of action of this drug.[18,19] Atracurium has two mechanisms of elimination, spontaneous decomposition by a self-destroying mechanism known as Hoffman clearance, and hydrolysis by non-specific esterases in the blood.[7] Renal or hepatic dysfunction, or extremes of age do not affect the systemic clearance of atracurium.[20-23]

Laudanosine, one of the major breakdown products of atracurium, has been reported to produce seizures in dogs after prolonged use at serum laudanosine concentrations of 17 mcg/mL or greater.[24] Concerns have been raised regarding the possibility of seizures caused by accumulation of this product with prolonged use, however, there have been no reports directly relating atracurium to seizure activity in humans. The measurement of serum laudanosine levels after prolonged atracurium infusions in patients with normal and impaired renal function has ranged from 1.2-5.1 mcg/mL.[25,26] Two cases of seizures have been reported with the use of atracurium infusions in critically ill, hemodialysis-dependent patients, however, the drug was not implicated in either situation; one patient had a closed head injury[27] and the other patient had hypoxia and viral encephalitis.[21] A laudanosine level taken in the latter case was 0.74 mcg/mL which is well below the toxic range established in dogs. Unfortunately, it is unknown whether this toxic level in dogs is similar to that in humans. Further study with cerebral monitoring is

Table I: Comparison of Pancuronium, Atracurium and Vecuronium

	PANCURONIUM (Pavulon®)	ATRACURIUM (Tracrium®)	VECURONIUM (Norcuron®)
ONSET	3-5 minutes	4-6 minutes	4-6 minutes
METABOLISM	20-25% hepatic	Hoffman elimination, ester hydrolysis	hepatic, spontaneous deacetylation
METABOLITES	Main metabolite 50% potency	inactive	inactive
EXCRETION	75-80% excreted unchanged in urine, metabolites also excreted in urine	metabolites excreted in urine and bile, 6% excreted unchanged in urine	75-80% biliary elimination, 15-25% excreted unchanged in urine
DURATION	40-60 minutes	15-30 minutes	15-30 minutes
ACCUMULATION	yes	minimal	some reports[32,35]
RENAL DYSFUNCTION	half-life increases	no effect	no effect
LIVER DYSFUNCTION	half-life may increase	no effect	half-life may increase
AGE	half-life may increase	no effect	half-life may increase
ADVERSE EFFECTS	minimal histamine release, some tachycardia, rarely supraventricular tachycardia	some histamine release at higher doses; metabolite laudanosine neurotoxic, but levels achieved clinically are well below toxic range	no histamine release
DOSE Bolus	0.04-0.1 mg/kg then 0.03-0.08 mg/kg PRN	0.4-0.5 mg/kg	0.08-0.1 mg/kg
Average Infusion	0.06 mg/kg/h	0.6 mg/kg/h	0.07 mg/kg/h
COST[17]/HOUR (70 kg patient)	$5.60	$18.70	$9.20

required to clarify this issue.

Intermittent versus Continuous Infusions

Pancuronium is commonly administered via intermittent bolus dosing. Long term use (greater than six days) of frequent bolus doses has been associated with accumulation, as well as severe and prolonged muscle weakness which was reversed after weeks to months of intensive physical therapy.[28,29] Continuous use of intermittent pancuronium requires constant monitoring to assess appropriate dosing and prevent excessive accumulation (Table II).

Continuous infusions offer an advantage over intermittent injections by maintaining a constant level of muscle relaxation with minimal fluctuations between paralysis and recovery.[8] Infusions are also more convenient and less labour intensive to administer than frequent bolus doses. Pancuronium has been administered via continuous infusion at rates ranging between 0.03-0.1 mg/kg/h (average 0.06 mg/kg/h); however, reversal of paralysis was prolonged taking 12-24 hours after discontinuation of the drug.[28,30,31]

The shorter duration of action of vecuronium and atracurium, and their lack of accumulation facilitates their administration via continuous infusion. The two drugs have not been directly compared to each other clinically, but have been examined individually in critical care patients. Atracurium has been administered with a loading dose of 0.4-0.6 mg/kg followed by an average infusion rate of 0.6 mg/kg/h (range 0.29-1.28 mg/kg/h) over periods of 2 to 219 hours.[21,25-27] Increased doses were required after 72 hours of therapy in one study.[26] Recovery times after discontinuation of the infusion were 30-75 minutes, although a prolonged recovery period lasting between 12 to 24 hours was observed in a patient who was hypophosphatemic.[27] Correction of this biochemical abnormality resulted in full recovery.

Vecuronium infusions have been studied in adults, infants and children for periods ranging from 6 hours to 12 weeks.[1,32,33,34] In these trials, a loading dose of 0.1 mg/kg was administered followed by a continuous infusion averaging

Table II: Management of Ventilated Patients Requiring Neuromuscular Blocking Agents (NMB)

1. Sedatives and analgesics are required and should be given on a regular schedule. Neuromuscular blocking agents have no analgesic and sedative properties; without sedation and analgesia, the patient is fully alert and is able to feel pain.
2. To assess neuromuscular function and prevent excessive dosing during prolonged use, the aid of a peripheral nerve stimulator (PNS) should be employed.

   If PNS is unavailable, additional NMB bolus doses or increases in infusion rates should be administered as soon as the patient begins to show signs of muscle movement (e.g. flickering of eyelids, wrinkling of brow, respiratory effort). Allow signs of muscle movement daily for continuous infusions.
3. All NMB inhibit the cough reflex; secretions must be removed manually. Suctioning should be performed regularly (e.g. every 2 hours) or as indicated by the amount of secretions present.
4. Patients should never be left unsupervised. Ensure all monitoring alarms are functioning. Post a sign above the patient's bed indicating that the patient is receiving an NMB.
5. To prevent drying and ulceration of the cornea (as patient has no blink reflex), instil artificial tears every 2-4 hours and tape eyes shut with clear tape.
6. To prevent skin breakdown and decubitus, turn patient frequently and keep bedding dry and free from wrinkles.
7. Unless contraindicated, prophylactic subcutaneous heparin 5000 units every 12 hours should be administered to prevent deep vein thrombosis.
8. Check pupillary reflexes hourly to assess neurological status.
9. Communicate with patients routinely; orientate them to time and place, explain various procedures, and reassure them that paralysis is only part of the treatment.[6] Allow for some periods of quiet time so the patient can sleep.
10. Be aware of physiologic conditions and drugs which can potentiate NMB effects[40]:

Physiologic Conditions	*Drugs*
Extremes of age	Inhalation anaesthetics (enflurane, isoflurane)
Respiratory acidosis	Antibiotics (aminoglycosides, colistin, vancomycin)
Hypothermia	Antiarrhythmics (verapamil, quinidine)

0.07 mg/kg/h (range 0.01-0.14 mg/kg/h). Results indicate that prolonged therapy may lead to increased dosing requirements.[1] Lower doses are required in patients with liver dysfunction as well as in the elderly.[18,19,34] Eldadah *et al*, in a study of 12 children, compared the effects of vecuronium when given via continuous infusion or intermittent hourly bolus doses.[34] The authors find no significant differences in muscle paralysis between the two regimens other than lower dosage requirements for patients receiving continuous infusions.

Time to complete recovery from paralysis with vecuronium averaged 28 minutes in patients who had received infusions for 15-68 hours.[33] However, there have been several cases of prolonged recovery times associated with this drug. In one series, seven patients with both renal and respiratory failure received vecuronium infusions for a mean of 20 hours. All patients experienced prolonged paralysis requiring 6-37 hours for full recovery.[32] Three of these patients had received concomitant therapy with tobramycin. Aminoglycosides may potentiate muscle paralysis from NMB due to their intrinsic neuromuscular blocking action.[29] A separate study of three patients who had been paralysed with vecuronium for periods of 7-22 days reported recovery rates from 5 days to greater than 22 days after discontinuation of therapy.[35] Factors which could have influenced prolonged paralysis included liver disease in one patient, and concomitant administration of aminoglycoside therapy in the other two patients. As well, none of the patients had been monitored for the effect of neuromuscular blockade (e.g. peripheral nerve stimulation) during their entire course.

Monitoring

Clinical observation of the patient, biochemical parameters (e.g. blood gases), and respiratory mechanics (e.g. respiratory rate, airway pressures) should be monitored closely to assess adequate relaxation during NMB use.[5] Peripheral nerve stimulators should ideally be used as an aid to evaluate neuromuscular function and prevent overdose in prolonged or repeated NMB administration.

Peripheral nerve stimulators assess muscle contractions evoked by an electrical stimulus.[7,36] There are four commonly used patterns of stimulation which can be used: single twitch, train-of-four (TOF), tetanus, and posttetanic stimulation.[36] The TOF is most commonly used in studies and clinical practice to assess NMB therapy as it is the easiest to visualize at the bedside without the aid of sophisticated transducers. With this method, 2 Hz electrical stimulations are applied to the ulnar nerve four times at 0.5-second intervals. The adductor pollicis (thumb) muscle is used to determine twitch height response. The ratio of the height of the fourth twitch as compared to the first is used to assess the percentage of nerves blocked.[36] The fourth twitch decreases and disappears initially, followed by the third, second and finally first response as the dose of the neuromuscular blocker is increased. For surgery, maintaining a 90-95% depressed first response to TOF stimulation with complete suppression of the last three responses generally represents an adequate

level of muscle relaxation.[36,37] For the mechanically ventilated patient, it has been recommended that infusions and bolus doses be adjusted to maintain a just-identifiable single first twitch.[35] This level of paralysis may not be necessary for all intensive care patients and should be guided by clinical judgement.

Without the aid of peripheral nerve stimulation, infusion rates should be titrated to just abolish signs of muscle movement, e.g. flickering eyelids, wrinkling brows, triggering ventilation.[38] For bolus dosing, additional doses need only be readministered when these signs appear. Careful monitoring and adjustment of dosing intervals is especially important in patients with end-organ dysfunction who require prolonged paralysis. Specific monitoring and management of patients receiving NMB are listed in Table II.

Upon discontinuation of NMB during mechanical ventilation, patients should be allowed to spontaneously regain muscle function.[39] Paralysis from non-depolarizing muscle relaxants may be acutely reversed by the cholinesterase inhibitors neostigmine, edrophonium, or pyridostigmine. These agents increase the amount of acetylcholine available in the synaptic cleft,[5] and are most commonly used to reverse muscle paralysis of short duration such as in surgery.[39] There is little information on the use of these agents during prolonged paralysis as discussed in this paper. Reversal of the intermediate acting agents vecuronium and atracurium is likely unnecessary.[5] If paralysis is profound, recovery after administration of cholinesterase inhibiters would be relatively slow or ineffective.[5,37]

In conclusion, bolus dosing of pancuronium remains an effective and economical means of paralysis for the majority of critically ill, ventilated patients. Vecuronium and atracurium, although more expensive, offer several advantages for patients who are requiring frequent pancuronium bolus doses for extended periods. Because they have shorter durations of action and minimal cumulative effects, atracurium and vecuronium can be administered by a continuous infusion. This provides a constant level of paralysis which is easily titratable. Also, these drugs have a higher cardiovascular safety margin, and changes in renal function do not necessitate dosage adjustments.

The choice between vecuronium and atracurium depends on the patient involved. Vecuronium may prove advantageous in the brain injured patient due to its lack of a potentially neurotoxic metabolite, while atracurium may be a better choice in patients with severe liver failure and in the elderly. The prolonged effects of vecuronium displayed in several case reports may indicate that atracurium is more appropriate for infusions of extended duration, although more studies are required. Constant monitoring of neuromuscular blockade, especially during prolonged paralysis, should be implemented to determine appropriate dosing and prevent excessive neuromuscular blockade.

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