

Reversal of neuromuscular blockade: current practice and future directions

BY FRANÇOIS DONATI, MD

Almost thirty years ago, residual paralysis was convincingly documented in a disconcerting proportion of patients (30%), despite an almost systematic use of anticholinesterase agents.¹ Since that time, even with the development of shorter-acting neuromuscular blockers, as well as pharmacological reversal and the more widespread use of nerve stimulation, residual paralysis is still a problem. Some even describe it as a public health problem, because residual neuromuscular blockade in the recovery room has been associated with episodes of hypoxia,² respiratory distress,³ airway obstruction,³ atelectasis,⁴ and patient discomfort,³ as well as increased mortality.⁵ It seems logical to assume that these complications are a direct consequence of the limited effectiveness of anticholinesterase agents in reversing neuromuscular blockade. Sugammadex, a compound that may soon become available, does not appear to have such limitations. This issue of *Anesthesiology Rounds* defines residual paralysis and discusses its physiological effects, incidence and the clinical trials describing its adverse effects. A review of the strategy that should be adopted to prevent residual paralysis, including the choice of neuromuscular blocking agent, monitoring and adequate reversal, follows. Finally, the pharmacology of sugammadex will be examined with attempts to foresee potential changes that the drug could bring to the practice of anesthesia.

PHYSIOLOGICAL CONSEQUENCES OF NEUROMUSCULAR BLOCKADE

Nondepolarizing neuromuscular blocking drugs inhibit nicotinic receptors at the neuromuscular junction. Although all skeletal muscles are targets of these drugs, clinically the most important are those playing a role in the respiratory system, including those that maintain upper airway patency and those that protect the tracheobronchial tree from fluid or solid aspiration. Most studies, designed to document the effects of neuromuscular blockers, measured the force of contraction of the adductor pollicis muscle in response to electric stimulation of the ulnar nerve; most often this was done in a train-of-four (TOF) mode, ie, 4 stimuli separated by a 0.5-sec interval. Several studies were able to establish various correlations between the TOF recordings obtained at the thumb and the respiratory effects of neuromuscular blocking agents. Since monitoring at the thumb is usually easy to perform in the operating room, knowledge of the correlation between the thumb and respiratory system helps the clinician to estimate the respiratory effects of neuromuscular blocking drugs. The TOF response is generally expressed as the fourth to first twitch ratio (TOF ratio).

Respiratory system

Patients can maintain a normal tidal and minute ventilation in spite of profound muscle paralysis characterized by the complete lack of TOF response.⁶ The underlying explanation is that the diaphragm, which plays a major role during quiet breathing, is particularly resistant to the effects of neuromuscular blockers; however, the vital capacity, essential for coughing, is reduced at low levels of neuromuscular blockade, ie, at a TOF ratio ~ 0.5. Similarly, maximum expiratory and inspiratory pressures are reduced when the TOF ratio is <0.7. Coughing, for example, involves muscles other than the diaphragm that are more sensitive to the effects of neuromuscular blockers. Thus, in order to achieve adequate vital capacity or maximum respiratory flow, an almost complete reversal of the blockade is necessary.

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Upper airway

Upper airway patency is dependent upon the coordinated action of several muscles, and it is difficult to consider them separately. Nevertheless, 3 muscles, the geniohyoid,⁷ the masseter^{8,9} and the genioglossus,⁶ are as sensitive as, and possibly more sensitive than the adductor pollicis to neuromuscular blocking agents when stimulated with the TOF mode. It is quite possible that other muscles ensuring upper airway patency are as sensitive, since the airway size is greatly reduced when TOF ratio ~ 0.7 .⁶ In volunteers, it was also noted that a TOF ratio >0.86 was required for a subject to hold a tongue depressor between his/her teeth against attempts by another person to remove it.⁹ Since the masseter muscle usually holds the lower jaw in place, it is generally recognized that a person with masseter paralysis could manifest upper airway obstruction. These data indicate that the upper airway muscles are especially sensitive to neuromuscular blockers.

Protection against aspiration

Swallowing is a very efficient mechanism to protect the tracheobronchial tree from aspiration of fluids or solids coming from the mouth or stomach. Upper esophageal sphincter tone measured by manometry reveals a reduction of $>50\%$ when the TOF ratio = 0.7. Following the administration of neuromuscular blocking agents, these values return to normal only at a TOF ratio >0.9 .¹⁰ Moreover, an increased incidence of laryngeal aspiration was noted when the TOF ratio was under the 0.9 threshold; thus, even shallow paralysis may increase the risk of aspiration.

DEFINING THE RESIDUAL PARALYSIS THRESHOLD

For many years, residual paralysis was defined by the presence of a TOF ratio <0.7 . This threshold was determined in the 1970s based on respiratory data obtained from a limited number of healthy volunteers.¹¹ In those studies, no significant decrease in inspiratory and expiratory pressures were noted at a TOF ratio = 0.7. However, these studies did not take into account interindividual variability, nor did they consider the effects of neuromuscular blocking agents on the maintenance of upper airway patency and swallowing. In the 1990s, a TOF ratio of 0.9 was suggested as a requirement to eliminate the possibility of residual neuromuscular blocking effects. This new threshold is now widely accepted in the definition of residual paralysis, and it emphasizes the significance of neuromuscular blockade effects on all components of the respiratory system, including the upper airway.^{9,10}

INCIDENCE OF RESIDUAL PARALYSIS

In 1979, a Danish group found a 30% incidence of residual paralysis in the recovery room when they measured the force of contraction following TOF stimulation. This result was obtained on the basis of the very conservative TOF threshold ratio of 0.7, which was accepted at the time.¹ The majority of

patients had received neostigmine, but neuromuscular monitoring was not a widespread practice. It should be noted that only a limited number of non-depolarizing neuromuscular blocking agents (pancuronium, d-tubocurarine, gallamine) were available at that time and all were long-acting. Further, if the current definition of residual paralysis, ie, a TOF ratio = 0.9, had been applied to those results, the incidence of residual paralysis would have reached 72%! Using the threshold of 0.9, subsequent studies found incidences ranging from 0% to 95%,¹² and a close examination of these studies identifies several risk factors associated with residual paralysis.

Duration of action of neuromuscular blocking agents

Unquestionably, the use of an intermediate-acting (atracurium, vecuronium, cisatracurium, rocuronium) instead of long-acting blocking agents reduces the incidence of residual paralysis, no matter what TOF threshold is chosen as a definition of residual paralysis.^{4,12} Nevertheless, the incidence of residual paralysis remains high, even with more recent drugs; for example, using the 0.9 threshold, a 41% incidence was reported associated with intermediate-acting agents, and even with the conservative threshold of 0.7, the incidence still reached 12%!¹² Long-acting agents are associated with incidences of 72% and 35%,¹² depending on the threshold selected. Therefore, although the switch to shorter-acting neuromuscular blocking drugs leads to a lower incidence of residual paralysis, the problem remains common and other actions are required to prevent its occurrence.

Monitoring

The impact of neuromuscular monitoring on the incidence of residual paralysis is less clear, considering that there are at least 2 types of devices and clinicians differ in the way they respond to the information provided. First, a distinction must be made between devices that only stimulate and those equipped with a sensor that also measures and records the response. When the device includes a stimulator only, the anesthesiologist must assess the magnitude of the elicited movement by visual or tactile means. Above a TOF ratio value ranging between 0.4 and 0.9, it is difficult, if not impossible, to detect whether the fourth twitch is less than the first. The use of this so-called "subjective" evaluation can explain, in part, the high incidence of residual paralysis reported in the literature.¹³ However, this situation should not occur when using devices equipped with electromyography, accelerometers, and displacement sensors; these devices accurately measure the moment when the TOF ratio reaches 0.9. In theory, if anesthesiologists keep patients intubated until a 0.9 threshold is reached or exceeded, the incidence of residual paralysis should equal zero; however, despite this clear logic, there was a 15% incidence of residual paralysis (defined as a TOF ratio <0.9) in a group of patients in whom accelerometers were used.¹⁴ Nevertheless, the same study demonstrated that the incidence climbs to 30%

when no monitoring is available. Although a benefit in association with monitoring has not been demonstrated in all studies,¹² it appears that the rigorous use of monitoring reduces the incidence of residual paralysis, as well as the need for maneuvers to maintain airway patency in the recovery room.¹⁵

Anticholinesterase agents

When neuromuscular blocking drugs with intermediate duration of action became available, some anesthesiologists thought they could dispense altogether with anticholinesterase agents to reverse neuromuscular blockade at the end of a procedure. In fact, in some countries and some hospitals, the use of anticholinesterase agents is not common. However, omitting the anticholinesterase agent gives rise to a high incidence of residual paralysis. For example, a 42% incidence, as defined by a 0.7 threshold, was reported with vecuronium, an intermediate-acting neuromuscular blocker.¹⁶ In the same facility, over several years, a follow-up of strict practices produced an impressive reduction in the incidence of residual paralysis from 62% in 1995 to 3.5% in 2004, as defined by a TOF ratio <0.9. Over the same period, the proportion of patients receiving anticholinesterase agents increased from 6% to 42%.¹⁶

Other factors

Residual paralysis appears to be more common in the elderly,⁴ while almost nonexistent in children. Elderly patients are also more subject to complications arising from residual paralysis.⁴ The administration of neuromuscular blocking agents as an infusion rather than intermittent boluses increases the risk of residual paralysis.¹² It is conceivable that administration of halogenated agents would lead to more residual paralysis than intravenous anesthesia, because halogenated agents potentiate neuromuscular blockade, but there are no studies to corroborate such a hypothesis.

CLINICAL EFFECTS OF RESIDUAL PARALYSIS

Neuromuscular blocking agents are not the only drugs likely to produce respiratory depression in a clinical setting; therefore, it is often difficult to pinpoint precisely the proportion of respiratory incidents specifically caused by residual paralysis. However, large-scale studies have indicated that residual paralysis increases the number of respiratory complications.

Hypoxemia

In a study involving 49 patients who received pancuronium, the incidence of hypoxemia (saturation reduced by >5% compared with baseline values) reached 60% in patients with a TOF ratio <0.7 and only 10% in the other patients.² A more recent study indicated that patients who were managed with an accelerometer during anesthesia had a higher TOF ratio in the recovery room. Hypoxemia and the need for interventions to improve oxygenation were also less frequent in those patients.¹⁵

Respiratory complications in the recovery room

Respiratory complications in the recovery room are relatively common and residual paralysis is not the only factor; however, the role of muscle relaxation in such events should not be underestimated. Recently, a group of patients with complications such as hypoxia, upper-airway obstruction and the need for an intervention to ensure adequate breathing, was compared with a control group with no such complications. The mean TOF ratio was 0.62 in the complications group, whereas it reached 0.98 in the control group.³

Atelectasis

One of the few randomized trials investigating the consequences of residual paralysis involved patients given pancuronium, atracurium, or vecuronium followed by neostigmine at the end of the procedure.⁴ As expected, a TOF ratio <0.7 was found more often in patients receiving pancuronium (30%), a long-acting neuromuscular blocker, than in those who received atracurium or vecuronium (5%), two intermediate-acting neuromuscular blockers. The incidence of atelectasis confirmed by chest X-ray 2 days after surgery was 3 times higher (17%) in patients who had residual paralysis (TOF ratio <0.7) in the recovery room than in the other patients (5%). This indicates that short-term residual paralysis can have long-term consequences.

Mortality

A Dutch study examined mortality attributed to anesthesia in over 800 000 patients, and the authors attempted to identify the factors predicting coma and death.⁵ Among the possible pre- or intra-operative actions having a positive influence on outcome, management issues such as the availability of an anesthesiologist were found to be important factors. One pharmacological treatment improved patient outcome: namely the administration of a reversal agent for neuromuscular blockade, which was associated with a 10-fold reduction in the incidence of mortality and coma.

PREVENTING RESIDUAL PARALYSIS

It is essential to avoid residual paralysis in the recovery room in extubated patients, and there is solid physiological and epidemiological evidence for this recommendation. Strategies to prevent residual paralysis are based on judicious use of anticholinesterase agents, and strict practice guidelines based on adequate monitoring whenever neuromuscular blocking drugs are administered (Table 1).

Anticholinesterase agents

Neostigmine, edrophonium, and pyridostigmine inhibit acetyl cholinesterase, allowing acetylcholine to have a more prolonged effect at the neuromuscular junction. Edrophonium has a rapid onset, but is not as effective as neostigmine for deep blocks. Pyridostigmine has a slow onset, which makes it ill-suited to the

TABLE 1: Strategy for neuromuscular blockade reversal at the end of a procedure

Number of TOF twitches at the adductor pollicis	Other data	If atracurium, cisatracurium, rocuronium, or vecuronium used	If rocuronium or vecuronium used and if sugammadex available
0	PTC = 0	Ventilate patient, wait for 4 twitches	Sugammadex, 8-16 mg/kg
0	PTC ≥ 1	Ventilate patient, wait for 4 twitches	Sugammadex, 4 mg/kg
1-3		Ventilate patient, wait for 4 twitches	Sugammadex, 2 mg/kg
4	TOF fade present	Neostigmine, 0.04-0.05 mg/kg*	Sugammadex, 2 mg/kg
4	TOF fade not detected by sight or touch	Neostigmine, 0.02-0.04 mg/kg* or edrophonium, 0.2-0.5 mg/kg*	
4	Documented T4/T1 ≥0.9	Reversal not required	Reversal not required

TOF = train-of-four; PTC = Post-tetanic count; T4/T1 = fourth to first response ratio following TOF stimulation.

* With atropine or glycopyrrolate

reversal of intermediate-acting neuromuscular agents.¹⁷ The discussion will therefore focus on neostigmine, which remains the most commonly used anticholinesterase agent, although many principles for its use also apply in a large part to edrophonium and pyridostigmine. Anticholinesterase agents are known for their parasympathomimetic effects, that must be neutralized by an anticholinergic agent – atropine or glycopyrrolate. The effectiveness of anticholinesterase agents is limited by a ceiling effect; for instance, neostigmine reduces the intensity of neuromuscular blockade in a dose-dependent manner up to 0.04 mg/kg -0.05 mg/kg, but a higher dose has no additional benefit.¹⁸ Therefore, doses up to 0.07 mg/kg add little; in addition, the agent must be injected only when sufficient spontaneous recovery is observed in order to attain a TOF ratio = 0.9 within a reasonable time, ie, 10-15 min following neostigmine. In fact, it is recommended to wait until there are 4 visible twitches following TOF stimulation before administering neostigmine;^{19,20} if the patient has not reached this degree of recovery, it is preferable to maintain anesthesia until there are 4 visible twitches before giving neostigmine. It is preferable to ventilate paralyzed patients rather than taking the risk of respiratory complications associated with residual paralysis. In cases where the 4 twitches appear equal by visual or tactile means, the possibility of residual paralysis should be considered. Given that human senses cannot detect fade when the TOF ratio is 0.4 or greater,¹³ even the administration of a reduced dose of an anticholinesterase agent, for instance neostigmine (0.02-0.04 mg/kg) or edrophonium (0.2-0.5 mg/kg), is preferable to doing nothing, when four twitches appear equal.

Choice of neuromuscular blocking agent

Long-acting neuromuscular blocking agents (pancuronium, doxacurium, etc.) should be avoided

in patients for whom extubation is planned at the end of the procedure. None of the intermediate-acting neuromuscular blockers (rocuronium, cisatracurium, vecuronium or atracurium) produce significantly less residual paralysis than the others. Nevertheless, they should be administered in doses such that, at the end of the surgery, spontaneous recovery is sufficient for the anticholinesterase agent to be effective. The anticholinesterase agent should be administered when 4 twitches can be seen following TOF stimulation. If the clinician chooses not to administer an anticholinesterase agent, it should be recognized that the presence of four seemingly equal responses to TOF stimulation does not necessarily mean that the T4/T1 ratio is >0.9. In fact, it is possible for the ratio to be between 0.4 and 0.9, indicating residual paralysis.^{13,16}

Monitoring

The limitations encountered with traditional monitoring, namely visual or tactile evaluations of a patient's responses to TOF stimulation, have led some authors to recommend the compulsory use of so-called "objective" monitoring, which involves a display of TOF ratio measurements.²¹ Unfortunately, currently available devices such as accelerometers and displacement sensors are often fragile and prone to breakage in everyday clinical practice.

FUTURE DIRECTIONS

Residual paralysis is the result of limitations in the pharmacology of the currently available neuromuscular blocking agents and their antagonists. Efforts have been made to develop short-acting neuromuscular blockers such as gantacurium, with a fast recovery profile that would, in practice, eliminate the possibility of residual paralysis. Currently, none of these products are available. An alternative approach has been to develop products

that accelerate neuromuscular recovery. Sugammadex is the result of these efforts, but despite its availability in Europe and other countries, it is not yet available in Canada or the United States.

Pharmacology of sugammadex

Sugammadex is a gamma-cyclodextrin, a ring-shaped molecule made up of 8 sugars with the addition of negatively-charged side chains. The rocuronium molecule, which is charged positively, has a size that fits well into the hole of the sugammadex molecule and is bound by the adjoining negative charges.²² As a result, sugammadex inactivates rocuronium molecules and indirectly decreases the intensity of neuromuscular blockade. Once bound, the sugammadex-rocuronium complex can be excreted by the kidneys. To a lesser extent, sugammadex also shows an affinity for vecuronium and pancuronium; however, it has no affinity for other neuromuscular blockers such as succinylcholine, atracurium, cisatracurium, and doxacurium.

Dosage

In clinical trials, the effectiveness of sugammadex has been studied in 3 situations:

- moderate blockade, ie, only 2 twitches are visible following TOF stimulation
- deep blockade, defined as no twitches seen after TOF stimulation and only 1-2 responses after post-tetanic count (PTC)
- 3–5 minutes after rocuronium administration, ie, when the failure of direct laryngoscopy and endotracheal intubation is noted.

The dose of sugammadex required depends on the depth of blockade and optimal results are obtained with 2, 4, and 16 mg/kg for moderate blockade,²³ deep blockade²⁴ and failure to intubate,²⁵ respectively. These dosages are valid for both rocuronium and vecuronium (Table 1). The recovery time following sugammadex administration is exceptionally fast, ie, approximately 2 minutes.

Role of sugammadex in clinical practice

It is too early to claim that sugammadex will revolutionize anesthesia, as some have predicted, but the high cost (~110-120\$CAD for a 200 mg dose, ie, ~2 mg/kg) will certainly restrict its generalized use. The advantage of this drug is that it is effective at every level of blockade, which is not the case with neostigmine; however, the situations where sugammadex would be particularly useful are those requiring relatively high doses, and thus greater expense. Actually, neostigmine is reasonably effective when it is administered at 2 visible twitches in response to TOF stimulation, and even more so if there are 4. In the case of deep blockade, neostigmine is not very effective, but the sugammadex dose required at that point reaches ≥ 4 mg/kg. As a result, it is still too early to recom-

mend the administration of large rocuronium doses during surgery while depending on a sugammadex safety net to reverse neuromuscular blockade. Furthermore, the potential for rapid antagonism by sugammadex should not lead to the imprudent use of neuromuscular blocking agents in the management of a difficult airway.

CONCLUSION

Residual paralysis undoubtedly contributes to a large proportion of postoperative respiratory complications such as hypoxia, hypoventilation, airway obstruction, atelectasis, and even death. Adequate monitoring, preferably based on the objective assessment of neuromuscular blockade, is recommended for a reliable diagnosis. However, monitoring cannot replace rigorous practices. Drugs have the same effects, whether monitored or not, and a reversal strategy must be planned from the initial administration of a neuromuscular blocking agent, which should have an intermediate duration of action and be given in a dose that is appropriate for the planned duration of the surgical procedure. Neuromuscular blockade should be monitored throughout the procedure to ensure sufficient recovery for neostigmine to have an optimal effect. Sugammadex could increase flexibility in managing the reversal of neuromuscular blockade, but it will not eliminate the need for appropriate clinical choices regarding dosage of neuromuscular blocking agents. Irrespective of the approach, the goal should be to bring the TOF ratio to ≥ 0.9 before the patient emerges from anesthesia and is extubated.

KEY POINTS

- Symptoms of residual paralysis can occur when the ratio between the fourth and the first twitch response following TOF stimulation (T_4/T_1) is < 0.9 .
- Residual paralysis, defined as a T_4/T_1 ratio < 0.9 , is relatively common; it is associated with episodes of hypoxia and upper airway obstruction.
- Ideally, neostigmine should only be administered if the number of twitches following TOF stimulation is 4.
- Abstaining from giving anticholinesterase agents is acceptable only if the T_4/T_1 ratio threshold is ≥ 0.9 and is documented by a measuring device.
- Sugammadex improves flexibility in the management of neuromuscular blockade reversal by allowing the reversal of intense blockade; however, it has an effect only on rocuronium and vecuronium.

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