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NEUROMUSCULAR BLOCKADE (GS MURPHY, SECTION EDITOR)

Management of Neuromuscular Blockade in the Elderly and Morbidly Obese Patient: What Does the Data Show?

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Abstract

Purpose of Review This review addresses considerations for optimal neuromuscular blockade management in the elderly and obese. The evidence for adjusting dosing for common neuromuscular blocking drugs (NMBDs) and their antagonists are discussed.

Recent Findings In the elderly patient, aminosteroidal NMBDs have a slower onset and prolonged duration of action. Aging has minimal effects on the organ-independent metabolism of the benzylisoquinolinium NMBDs. Slower circulatory times and reduced renal function in the elderly also have implications on the clinical effects of NMBD antagonists. Since drug clearance and distribution is not the same in obese and in lean patients, dosing based on the total body weight (TWB) will result in excess NMBD administration. Various dosing scalars such as ideal body weight (IBW), lean body weight (LBW), and fat-free mass (FFM) have been proposed but each has its own limitations. NMBDs should be dosed based on ideal body weight in obese patients. Optimal sugammadex dosing in obese patients remains controversial while neostigmine administration should not exceed 5 mg.

Summary Elderly and obese patients have an increased risk of developing complications in the perioperative period, particularly when NMBDs are administered. Vigilance, careful titration, and quantitative monitoring are warranted to care for these challenging patients.

Keywords Residual neuromuscular blockade · Neuromuscular blockade · Patient safety · High risk populations

Introduction

Neuromuscular blocking drugs are used to (i) improve the quality of intubating conditions [1], thereby, decreasing the incidence of vocal cord injury during laryngoscopy [2], and (ii) to improve surgical conditions [3, 4]. As with any medication, the use of neuromuscular blocking drugs (NMBDs) is not without risk. Postoperative residual weakness from NMBDs persists as a patient safety threat and the anesthesia community has been slow to adopt evidence-based practices that could address this iatrogenic complication [5]. Residual neuromuscular blockade can have significant consequences with problems ranging from feelings of subjective weakness during time in the recovery room [6] to the need for reintubation and unanticipated postoperative complications that require admissions to the intensive care unit [7].

Fortunately, several strategies have emerged to combat postoperative residual neuromuscular blockade that include the avoidance of longer acting NMBDs such as pancuronium in favor of short acting agents [8], the use of quantitative neuromuscular monitoring, and routine administration of NMBD antagonists such as neostigmine or sugammadex [9, 10]. A recent international panel of experts has also released a comprehensive consensus statement detailing the call for quantitative neuromuscular monitoring as an evidence-based approach to reduce postoperative residual neuromuscular blockade [11••]. The use of quantitative monitoring can not only reduce the incidence of postoperative neuromuscular blockade, but also its associated complications [12–15].

This article is part of the Topical Collection on *Neuromuscular Blockade*

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In this article, we will briefly review important considerations for managing neuromuscular blockade in two high-risk populations—the elderly and the obese patients. We will address the physiologic changes that occur with both of these populations and the impact these changes have on the pharmacokinetics of NMBDs and their antagonists. Finally, we will discuss evidence-based strategies that can be utilized to provide optimal neuromuscular blockade management and improve perioperative care for these important patient populations.

Pharmacokinetics in the Elderly Patients

Aging is associated with several important factors that affect the pharmacokinetics of drugs commonly used in the perioperative setting. Total body water decreases the effective central compartment which can lead to higher peak concentrations following boluses or rapid infusions [16]. Advancing age is associated with decreases in clearance and central distribution volume (Fig. 1) [17]. Aging is associated with decreases in total body water and increases in total body fat (as % of TBW). Increase fat content in the elderly results in increase of the volume of distribution of lipophilic drugs, but the volume of distribution of water soluble drugs is decreased. Cardiac output also decreases with age [18], resulting in slower circulation times and slower equilibration within the plasma, and delayed onset of the peak onset of drug effects compared with young adults. While this results in lower tissue perfusion and slower drug transport, disproportional decreases in hepatic and renal blood flow also restrict drug metabolism and elimination that prolongs drug duration of action [16]. Elimination of drugs commonly occurs via conversion to inactive metabolites in the liver, excretion in bile, or elimination through the kidneys. Clearance of drugs eliminated by the kidneys may be reduced by 50% in elderly and drugs with high hepatic clearances may be affected by the age-related decrease in hepatic blood flow [16].

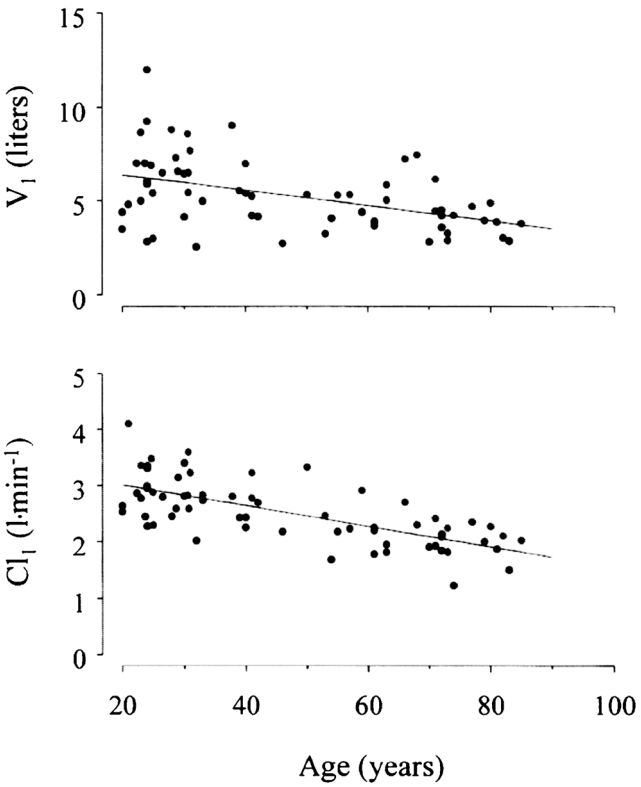


Fig. 1 The individual Bayesian estimates of V_1 and Cl_1 as a function of age (dots). The linear relationship between age, V_1, and Cl_1 (lines) are estimated by linear regression. V_1, volume; Cl_1, clearance. Reproduced from Minto CF, et al.: Influence of age and gender on the pharmacokinetics and pharmacodynamics of remifentanil. I. Model development. Anesthesiology 1997; 86(1): 10–23, with permission from Wolters Kluwer Health, Inc. Accessible at https://anesthesiology.pubs.asahq.org/article.aspx?articleid=2028700

Neuromuscular Blockade in the Elderly Patient

As aging is associated with increasing comorbidities, general anesthesia in the elderly population can be associated with increased risk [19]. While adequate preoperative evaluation, risk stratification, and optimization can mitigate this risk, anesthesiologists must also be intimately familiar with physiologic changes associated with aging and the impact these alterations can have on drugs routinely utilized during intraoperative care. NBMD administration in any patient population has been associated with a variety of complications such as oropharyngeal dysfunction [20], critical respiratory events [7, 21], and prolonged recovery times [22]. Unfortunately, the primary mechanism of such complications, postoperative residual neuromuscular blockade, occurs with greater frequency in the elderly when compared with younger patients [23••]. With this in mind, the incidence of postoperative residual neuromuscular blockade could potentially increase over time as a result of proportional increases in the elderly population presenting for surgery [24]. As such, vigilance and a thorough understanding of the age-related changes in pharmacokinetics of this at-risk patient population are certainly warranted.

The Aging Neuromuscular Junction

The neuromuscular junction (NMJ) has been described as "one of the most studied and best understood synapses" [25•]. Understanding the NMJ in the elderly patient is the first step to optimal neuromuscular blockade management during general anesthesia in this population. Skeletal muscle mass and strength progressively declines with age as the number of muscle fibers declines [26] with a corresponding increase in fat [27]. Additionally, neuromuscular transmission proves to be significantly less efficient with age as the number of motor

neurons and myelinated axons decrease [28] and compensatory mechanisms result in a proliferation of weaker, unstable motor neurons at new sites [29] that do not allow for effective synaptic contact at the neuromuscular junction [30]. Increases in neurotransmitter release also represent compensatory measures [31]; however, the summation of these age-related changes results in a progressive decline in the force generated from skeletal muscle [32].

Succinylcholine

Succinylcholine is metabolized via the enzyme butyrylcholinesterase. As only 10% of intravenously administered succinylcholine reaches the neuromuscular junction, age-related changes to butyrylcholinesterase activity do not appear to have an impact on metabolism and duration of action in the elderly. The onset neuromuscular blockade induced by succinylcholine is preceded by fasciculations from this agent's antidromic effects [33]. With less skeletal muscle mass, this response may be attenuated in the elderly.

Aminosteroidal NMBDs

Aminosteroidal NMBDs (pancuronium, vecuronium, and rocuronium) are metabolized and eliminated through the hepatic and renal systems. As such, recovery from this class of medications has been found to be prolonged in the elderly as overall clearance is reduced [34–37]. Such age-related changes to pharmacokinetics warrant reductions in maintenance dosing as plasma clearance is reduced and elimination half-life is significantly prolonged. Careful titration based on quantitative neuromuscular monitoring is paramount when utilizing aminosteroidal NMBDs in the aging patient as alterations in pharmacokinetics can result in prolonged effects from this class of medications [38].

Benzylisoquinolinium NMBDs

Unlike the amino steroidal NMBDs, benzylisoquinolinium NMBDs are metabolized through organ-independent mechanisms. Atracurium is metabolized via plasma esterase-mediated hydrolysis and Hofmann degradation, a nonenzymatic reaction that is a function of pH and temperature. Smaller, early studies of atracurium have yielded conflicting results when determining the effects of age on pharmacokinetics and pharmacodynamics [39, 40]. Cisatracurium, the cis-isomer of atracurium, is primarily metabolized by Hofmann degradation. Small differences have been reported in the recovery profile, onset time, and elimination half-life in the elderly versus younger cohorts with cisatracurium due to increases in volume of distribution [41]. With organ-independent metabolism, these slight differences in pharmacokinetics and pharmacodynamics result in little clinical discrepancies when utilizing cisatracurium and atracurium in the elderly.

Mivacurium is a short-acting benzylisoquinolinium NMBD that is metabolized by the enzyme butyrylcholinesterase and has recently been reintroduced to the United States market. Clearance and elimination half-life has not found to be significantly different between elderly and young adult cohorts [42]. However, reductions in butyrylcholinesterase activity in the elderly [43] can account for prolonged duration of action in clinical settings [44].

NMBD Antagonists

Neostigmine and edrophonium are acetylcholinesterase inhibitors. This inhibition results in an increase in acetylcholine concentration at the neuromuscular junction that competitively displaces NMBD bound to postsynaptic receptor sites [25•]. Edrophonium is primarily excreted by the kidney and its clearance is reduced in the elderly [45]. However, this increase in plasma concentrations did not affect the duration of NMBD antagonism. Neostigmine also has delayed clearance in the elderly with a resultant prolonged duration of action [46]. While such prolongation of action could imply that the elderly may be less likely to develop postoperative residual weakness following NMBD administration, the contrary has been demonstrated [23••] as the etiology of this complication is truly multifactorial.

Unlike the acetylcholinesterase inhibitors, sugammadex binds directly to aminosteroidal NMBD in the plasma, creating a concentration gradient that displaces these drugs from their site of action at the neuromuscular junction [47] into the plasma. While the prolonged circulatory time found in older patients can result in slightly delayed recovery from neuromuscular blockade after sugammadex administration [48], the dose of sugammadex does not need to be adjusted in the elderly patient and this antagonist can be safely used in this patient population [49•].

Collectively, NMBD potency in elderly patients is largely unchanged although the onset and recovery from neuromuscular blockade can be prolonged, particularly when aminosteroidal NMBDs are utilized as these medications undergo organ-dependent metabolism (Table 1). Acetylcholinesterase inhibitors and sugammadex can be safely used in the patient population without significant dosing adjustments (Table 2). Additionally, vigilance is warranted as this patient population has less physiologic reserve and incomplete recovery from neuromuscular blockade after surgery could ultimately lead to a catastrophic complication such as aspiration pneumonia [50]. We recommend the use of quantitative monitoring any time NMBDs are utilized; however, such monitoring may prove particularly worthwhile in this vulnerable population as pharmacokinetics can be significantly altered.

Table 1 Neuromuscular blocking drugs in high-risk populations

Drug	Elderly patient considerations	Obese patient dosing
Succinylcholine	Unchanged onset and duration, less fasciculations from less skeletal muscle mass	Dose based on TBW
Pancuronium	Decreased clearance and prolonged recovery, active metabolites can cause RNMB	Increased dosing requirements to maintain blockade, active metabolites can cause RNMB
Vecuronium	Prolonged recovery and slower onset time	Delayed clearance from reduced hepatic blood flow, dose based on IBW
Rocuronium	Prolonged recovery from reduced clearance	Conflicting evidence, recommend basing on IBW
Atracurium	Organ-independent elimination results in minimal changes in clinical effect	Conflicting evidence, recommend basing on IBW
Cisatracurium	Organ-independent elimination results in minimal changes in clinical effect	Conflicting evidence, recommend basing on IBW
Mivacurium	Prolonged effect from decreased butyrylcholinesterase activity	No changes in clinical effects when based on TBW vs IBW

TBW, total body weight; *IBW*, ideal body weight; *RNMB*, residual neuromuscular blockade

Pharmacokinetics in the Obese Patient

Obesity also results in significant alterations to the pharmacokinetics. Increasing fat content in this population also corresponds with increases in total body weight and such factors can impact volume of distribution for many drugs [51, 52]. Absolute drug clearance may be increased in obese versus nonobese patients. While clearance increases in a linear fashion with lean body weight, clearance increases unpredictably with increases in total body weight [53]. Additionally, obese patients experience increases in cardiac output, total blood volume, and alterations to regional blood flow. Even in the setting of normal liver function tests, obese patients may have occult hepatic histopathology [54–56] and hepatic blood flow corrected for total body weight is actually reduced in obese patients to approximately half that of predicted [57]. Such factors have a significant impact on pharmacokinetics and make predicting clinical effects of many drugs particularly challenging [51, 52, 58].

Dosing in the Obese Patient

In obese patients, dosing based on the total body weight (TWB) will result in overdoing. Various dosing scalars such as ideal body weight (IBW), lean body weight (LBW), and fat-free mass (FFM) have been proposed but each has its own limitations [59]. As TBW approaches morbid obesity, LBW starts to decrease in size.

Neuromuscular Blockade in the Obese Patient

Obese patients present with a number of unique concerns as the additional weight causes significant physiologic perturbations. This group has a decreased functional residual capacity and is intolerant to prolonged periods of apnea that can accompany endotracheal intubation [60]. As such, selecting the appropriate neuromuscular blocking drug and dose is paramount to utilizing this class of medications to facilitate securing the airway [60]. Even after adequate period preoxygenation for 3 min, obese and morbidly obese patients are prone to develop prolonged periods of oxygen desaturation, compared with normal-sized patients, when securing the airway is anticipated to take longer than 3 min and effective mask ventilation is potentially difficult [61••].

Obstructive sleep apnea is also more prevalent in obese patients and serves as a significant risk factor for developing postoperative pulmonary complications [62, 63]. Obesity is associated with a number of diseases that have important perioperative implications. Conditions such as hypertension, diabetes, cardiopulmonary disease, and obstructive sleep apnea are more prevalent among this population [64, 65]. The summation of these physiologic changes of obesity combined with

Table 2 Neuromuscular blocking antagonists in high-risk populations

Drug	Elderly patient considerations	Obese patient dosing
Neostigmine	Reduced clearance with prolonged duration of antagonism	"Ceiling effect" caps dose at 5 mg, can take longer to achieve adequate recovery
Edrophonium	Reduced clearance with no change in duration of antagonism	No data
Sugammadex	Delay in antagonism from decreased cardiac output and longer circulatory time	Manufacturer recommends TBW; however, IBW + 40% may be appropriate

co-existing diseases ultimately reduces the physiologic reserve of these patients and can reduce the margin of safety for NMBDs and their antagonists. As such, it is imperative that the anesthesiologist be familiar with the implications obesity has on establishing, maintaining, and antagonizing neuromuscular blockade.

Succinylcholine

The duration of action of succinylcholine is predominantly determined by the activity of butyrylcholinesterase [66] and the volume of extracellular fluid [67]. With both of these parameters being increased in obesity, succinylcholine dosing is based on total body weight [68]. Dosing succinylcholine in this fashion, rather than based on ideal body weight, results in a more profound block that improves intubating conditions without significantly increasing postoperative myalgia [69]. While the optimal intubating dose of succinylcholine has been heavily scrutinized in the general population [70–72], the utilization of total body weight in obese patients is an evidence based practice that can facilitate endotracheal intubation. However, this approach will result in a prolonged duration of neuromuscular block and apnea.

Aminosteroidal NMBDs

The neuromuscular blocking drugs are polar drugs, and their volume of distribution is classically thought to be limited to a volume roughly equivalent to a portion of the extracellular fluid space ~ 150–450 mL/kg [73] and IBW is a useful predictor of pharmacokinetic behavior of neuromuscular blocking drugs. As longer acting NMBDs with active metabolites such as pancuronium have been implicated in postoperative residual weakness, utilization of shorter acting NMBDs is recommended [52].

Vecuronium is primarily distributed in lean body mass and dosing should also be based on ideal body weight [74]. When based on total body weight, recovery is predictably prolonged [74, 75]. Rocuronium has a quarternary ammonium group that limits its distribution outside the extraceulluar fluid. While obese patients have increases in extracellular fluid, there are conflicting reports on how obesity impacts dosing regimens. Leykin et al. have demonstrated that rocuronium duration of action is doubled when based on total body weight versus ideal body weight [76]. As such, dosing rocuronium based on ideal body weight and guided by quantitative neuromuscular monitoring can help minimize the risk of developing postoperative residual weakness in this high risk population.

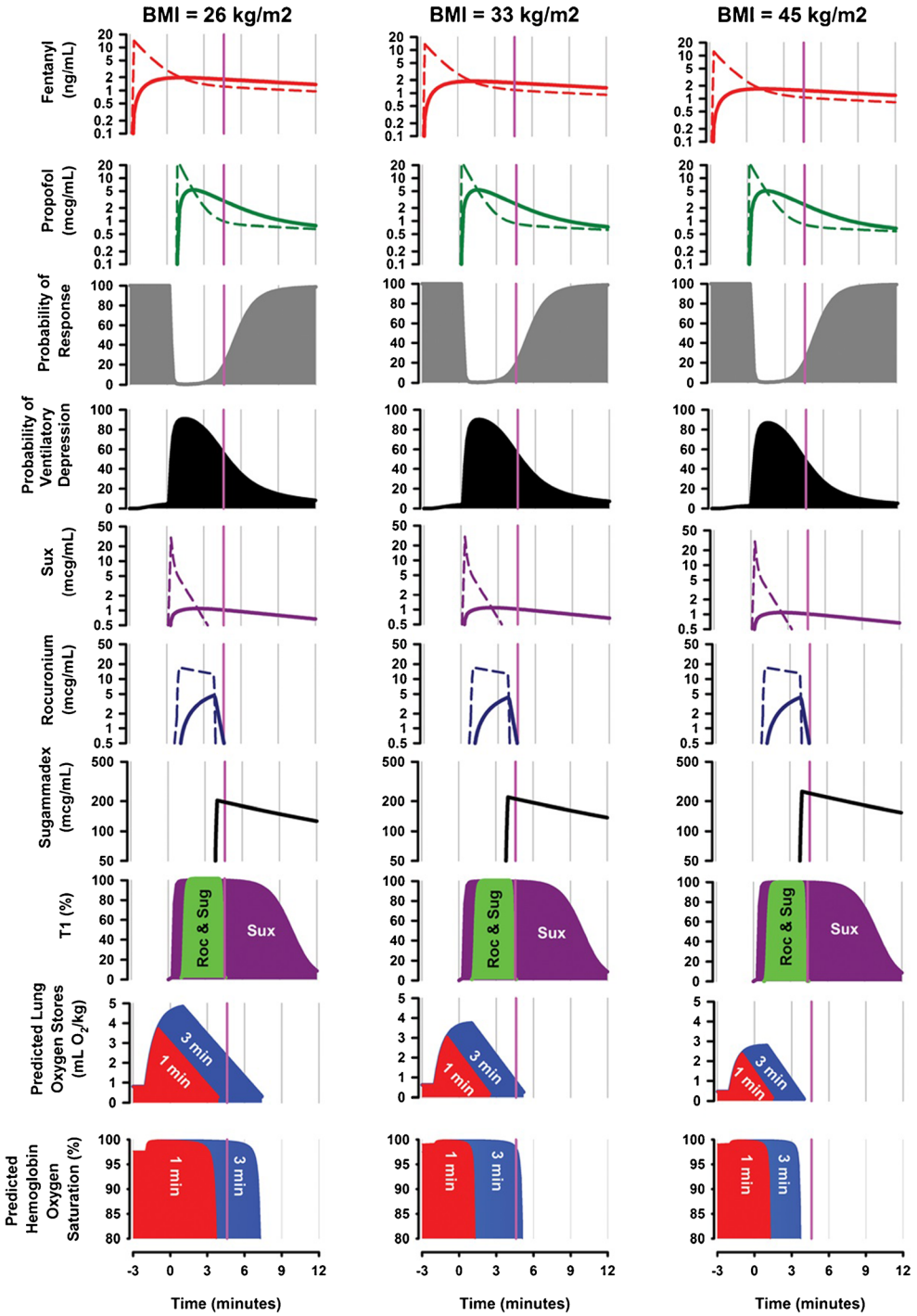
Benzylisoquinolinium NMBDs

Barrio et al. described no differences in clinical effect when dosing the short-acting drug mivacurium on total body weight in obese patients when compared with those with normal weight [77]. However, the literature for atracurium and cisatracurium has proven to be inconsistent when describing the effects of obesity. It was initially felt that duration of action of atracurium is not prolonged in obese patients as a result of its organ-independent elimination [75, 78]. Although, atracurium (and cisatracurium) dosing in the obese patient was initially based on total body weight [79, 80], but it was noted that such dosing resulted in a prolonged duration of action for atracurium and cisatracurium [81, 82]. It is, therefore, advisable that dosing should be based on ideal body weight. Similar to the aminosteroidal NMBDs, quantitative monitoring and dosing based on ideal body weight is likely prudent to avoid postoperative residual weakness.

NMBD Antagonists

Acetylcholinesterase inhibitors has a “ceiling effect” once the maximal inhibition of the acetylcholinesterase enzyme is achieved [83]. Dosing of anticholinesterases is typically based on the ideal body weight with a maximum dose of 5 mg [84]. Dosing regimens based on total body weight do not significantly shorten recovery times [85]. Following administration of neostigmine at 25% of spontaneous recovery of first twitch height of train-of-four, the time to recover to a train-of-four ratio to 0.5 can be similar in obese patients and patients with normal weights. However, the average time to achieve full recovery (train-of-four ratio > 0.9) is prolonged in obese versus normal weight patients (28.8 vs 22.75 min, respectively) [86]. As experienced anesthesiologists are unable to determine the presence of fade once the train-of-ratio reached ~ 0.4, patients may be prematurely extubated in such scenarios [87]. Unfortunately, even shallow levels of residual neuromuscular blockade (train-of-four ratios between 0.7 and 0.9) can pose significant risk to patients as oropharyngeal dysfunction can lead to aspiration events [23••]. Quantitative neuromuscular monitoring is the only reliable method to determine adequate recovery from neuromuscular blockade [11••].

Obesity has important implications on dosing sugammadex to antagonize aminosteroidal NMBDs. The manufacturer currently recommends dosing the drug based on total body weight. However, the cost of this drug is higher than neostigmine and dosing based on ideal body weight, total body weight, or some variation could carry significant financial implications [88]. With a low volume of distribution, sugammadex is restricted to the vasculature, suggesting dosing based on ideal body



weight may be appropriate [89]. However, such dosing regimens have resulted in instances of postoperative residual neuromuscular blockade [90, 91]. More recently, dosing this antagonist based on ideal body weight + 40% has yielded promising results as a compromise between ideal versus total body weight regimens [92, 93]. When deviating from manufacturer recommendations, quantitative monitoring is essential to confirming adequate recovery and that more antagonist are not needed prior to tracheal extubation. Comparable to patients with normal weight, sugammadex restores neuromuscular function faster in obese patient than neostigmine and reduces the incidence of postoperative residual neuromuscular blockade [94]. Sugammadex also has the novel

◀ **Fig. 2** Predicted onset and duration of selected drug effects administered to a normal (body mass index (BMI) = 26 kg/m^2), obese (BMI = 33 kg/m^2), and morbidly obese (BMI = 45 kg/m^2) individuals. Induction drug sequence was fentanyl followed 3 min later by propofol followed by either succinylcholine or rocuronium. Relaxants were administered 1 min after propofol administration. Time = 0 min is defined as the time propofol was administered. Rocuronium was reversed 3 min later with sugammadex. Doses of each drug are presented in Table 2. Predicted effects include probability of response based on the Observer's Assessment of Alertness/Sedation (OAA/S) scale, 15 probability of ventilatory depression defined as a respiratory rate of ≤ 4 breaths/min in an unstimulated state, neuromuscular blockade is defined as probability of the first twitch depression (T1%) in patients who received succinylcholine or rocuronium/sugammadex paradigm and predicted hemoglobin oxygen saturation in the presence of apnea. The solid lines represent plasma concentrations. The dashed lines represent the effect-site concentrations. Predicted oxygen saturation (Spo2) is presented as a function of the duration of preoxygenation before drug induced apnea. Red and blue represent 1 and 3 min of preoxygenation with an Fio2 of 0.6, a respiratory rate of 14 breaths/min, and an alveolar tidal volume of 3 mL/kg. Alveolar tidal volume is defined as the anatomic dead space volume subtracted from the tidal volume. The pink vertical lines represent the time points at which neuromuscular blockade is completely reversed with sugammadex. Reproduced from Naguib, M., et al., The myth of rescue reversal in "can't intubate, can't ventilate" scenarios. Anesth Analg, 2016. **123**(1): p. 82–92, with permission from Wolters Kluwer Health, Inc. Accessible at https://journals.lww.com/anesthesia-analgesia/fulltext/2016/07000/The_Myth_of_Rescue_Reversal_in__Can_t_Intubate,.12.aspx.

ability to reverse profound levels of rocuronium-induced blockade in the dreaded "can't intubate, can't ventilate (CICV)" scenario. However, simulation models have suggested that this pharmacologic rescue would not prevent dangerous levels of hypoxia in the obese patient and cannot be used as a substitute for basic airway management skills (Figs. 2 and 3) [61••].

Conservative managements strategies designed to reduce the risk of postoperative residual neuromuscular blockade in obese patients involve dosing NMBDs based on ideal body weight (Table 1), using quantitative neuromuscular monitoring, and administration of reversal agents based on the train-of-ratio response (Table 2).

Conclusion

Both elderly and obese patients present important concerns that warrant careful consideration in the perioperative period. Optimal neuromuscular blockade management is just one component to providing safe anesthetic care and is particularly important in these high risk patients with limited physiologic reserve. Unfortunately, the incidence of postoperative residual weakness remains unacceptably high and largely unchanged [95, 96] as the anesthesia community collectively possesses significant gaps in knowledge pertaining to fundamentals of neuromuscular blockade [97]. As such, vigilance, careful titration of NMBDs, and the utilization quantitative monitoring can help the anesthesiologist navigate such challenging scenarios and prevent potentially catastrophic postoperative residual weakness in elderly and obese patients.

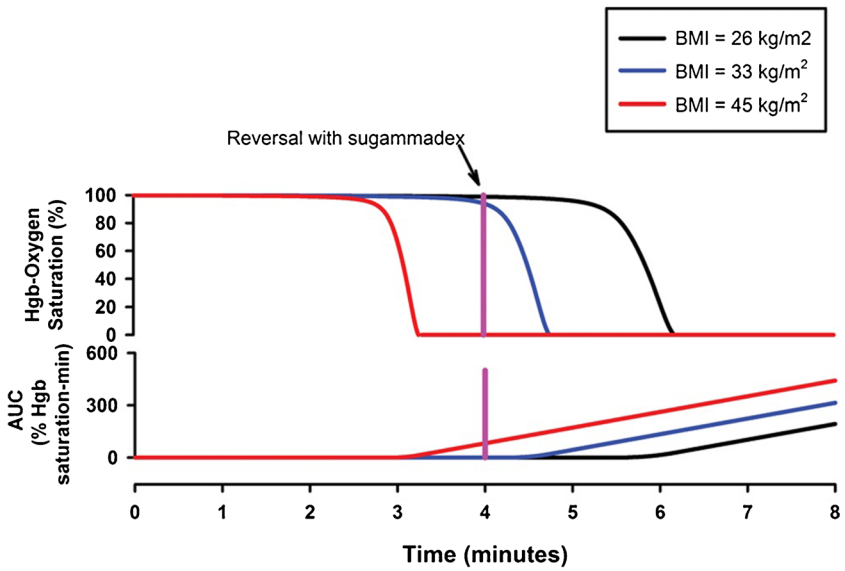


Fig. 3 A comparison of hemoglobin (Hgb) oxygen saturations (top plot) and area under the curve (AUC) for saturations < 90% over time (bottom plot) for 3 body sizes using simulated data presented in Fig. 3. The saturation versus time predictions assumed 3 min of preoxygenation with an Fio2 of 0.6 (before time = 0 min). Time 0 represents the induction time. The vertical pink line represents the time point at which neuromuscular blockade was reversed with sugammadex (4 min after induction with propofol). This timing mimicked the scenario of preoxygenation, followed by induction of anesthesia, onset of apnea (time = 0 min), administration of a neuromuscular-blocking agent at time = 1 min, and reversal of neuromuscular blockade at time = 4 min. Reproduced from Naguib, M., et al., The myth of rescue reversal in "can't intubate, can't ventilate" scenarios. Anesth Analg, 2016. **123**(1): p. 82–92, with permission from Wolters Kluwer Health, Inc. Accessible at https://journals.lww.com/anesthesia-analgesia/fulltext/2016/07000/The_Myth_of_Rescue_Reversal_in__Can_t_Intubate,.12.aspx.

Compliance with Ethical Standards

Conflict of Interest J Ross Renew has received research support through a grant from Merck (with funds to Mayo Clinic). Mohamed Naguib has served as a consultant for GE Healthcare in 2018.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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