

Neuromuscular blockade in the elderly patient

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Abstract: Neuromuscular blockade is a desirable or even essential component of general anesthesia for major surgical operations. As the population continues to age, and more operations are conducted in the elderly, due consideration must be given to neuromuscular blockade in these patients to avoid possible complications. This review considers the pharmacokinetics and pharmacodynamics of neuromuscular blockade that may be altered in the elderly. Compartment distribution, metabolism, and excretion of drugs may vary due to age-related changes in physiology, altering the duration of action with a need for reduced dosage (eg, aminosteroids). Other drugs (atracurium, cisatracurium) have more reliable duration of action and should perhaps be considered for use in the elderly. The range of interpatient variability that neuromuscular blocking drugs may exhibit is then considered and drugs with a narrower range, such as cisatracurium, may produce more predictable, and inherently safer, outcomes. Ultimately, appropriate neuromuscular monitoring should be used to guide the administration of muscle relaxants so that the risk of residual neuromuscular blockade postoperatively can be minimized. The reliability of various monitoring is considered. This paper concludes with a review of the various reversal agents, namely, anticholinesterase drugs and sugammadex, and the alterations in dosing of these that should be considered for the elderly patient.

Keywords: anesthesia, elderly, drugs, pharmacokinetics, pharmacodynamics

Introduction

Elderly patients are a continually growing population of health care consumers increasingly likely to need access to the highest quality health care.¹ Quantifying this problem may be difficult, as the definitions of “elderly” have shifted from 65 to 75 years and beyond. The Working Party into the Perioperative Care of the Elderly 2014 even advocated for the abandonment of using chronological age to define “older.”² Over time, the process of aging influences the cellular process, leading to the natural physiological decline of the cell’s capability of division and function, finally leading to cell death. This results in ~1% functional decline per year after 40 years of age.²

However, researchers rarely conduct large randomized controlled trials specifically in elderly patients and often exclude them from other trials.³ The reasons are multifactorial, but ultimately it is because elderly patients have multiple comorbidities and take many medicines, many of which cannot be stopped. These factors would introduce numerous confounding variables. As a result of the paucity of studies, predicting the action of drugs in the elderly can be difficult.^{4,5}

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In relation to anesthetic drugs, some things are known. The elderly population is more sensitive to neuromuscular blocking agents (NMBAs) due to alterations mainly in pharmacokinetics that occur with advancing age. Reduced volume of distribution (Vd) and clearance by age result in an increase in the concentration of drugs in blood. When hydrolysis by plasma cholinesterase is responsible for the elimination of muscle relaxants such as suxamethonium and mivacurium, an age-related decrease in this enzyme level causes a longer duration of action.⁶ The proper management of NMBAs in all patients (including the elderly) is important for several reasons. First, appropriate depth of the neuromuscular blockade is needed to facilitate surgery, in particular laparoscopic and open operations,⁷ as well as required in some forms of airway management, including both (temporarily) in mask ventilation and (sustained in) tracheal intubation.⁸ Second, residual neuromuscular blockade can lead to postoperative respiratory complications.⁹ Third, from the results of the Fifth National Audit Project in the UK (NAP5), NMBAs contribute to the genesis and impact of accidental awareness during general anesthesia: almost all (97%) cases of possible awareness involved patients who received NMBAs.^{10–12} Finally, rapid reversal may be needed in the management of failed tracheal intubation. The largest audit of anesthetic activity in the UK recently confirmed that ~46% of all general anesthetics involve the use of NMBAs.¹³

Age-related changes occur in all organs but the reduction is especially pronounced in the cardiovascular, respiratory, renal, hepatic, and central nervous system.¹⁴

Pharmacology in the elderly

Pharmacokinetics

Distribution

Once a drug enters the bloodstream, it does not stay there. Rather it moves to different parts (compartments) of the body. The Vd of a drug is influenced by factors such as protein binding (only unbound drug can be distributed), pH, molecular size, and solubility. The amount of drug present to produce an effect is proportional to its concentration at receptor sites. Therefore, the above changes in drug distribution can affect the response to the same drug doses.¹⁵ Lipid-soluble drugs have a higher Vd because they can cross the selective lipophilic cellular membrane. As people get older, lean body mass and total body water decrease, in contrast to body fat. Body fat can soak up fat-soluble drugs.¹⁵ Therefore, fat-soluble drugs will tend to have a higher Vd in elderly patients in contrast to younger

patients. Conversely, water-soluble drugs and drugs mainly distributed in the extracellular fluid will have a lower Vd.⁵ In older people, smaller doses (by total body weight) of muscle relaxant are needed.⁵

Another change that occurs with aging is in protein binding. Distribution can occur only when the drug is unbound as big drug–protein complexes cannot cross the selective membranes. Plasma albumin concentration tends to decrease with age and structural protein changes that occur with age lead to decreased efficiency in albumin binding, to as little as 20% by the age of 70 years.¹⁶ Therefore, in the elderly, as less drug is protein bound, the free drug concentration will increase, enabling more drug to reach its receptors and thus have a pharmacologic effect.^{4,5}

Plasma concentrations of NMBAs corresponding to a fixed degree of paralysis are not modified by aging and the concentration–response relationships remain usually unchanged, suggesting that aging does not influence the pharmacodynamic component of the NMBAs.^{17–19} Parker et al²⁰ reported that the rate constant of exit from the effect compartment (k_{eo}) decreases by 0.001 per minute per year, or ~0.03 per minute over three decades. Speculatively, this could be due to the effect of age on the peripheral circulation, leading to declining blood flow.

Metabolism

The liver is the primary organ responsible for drug metabolism. Liver mass decreases with age. Hepatic blood flow (HBF) decreases by 10% per decade. The capacity to metabolize drugs decreases. This decreased synthetic and metabolic activity as well as reduced HBF^{4,5} can alter the pharmacokinetic and pharmacodynamic properties of many drugs used during anesthesia, including NMBAs.

The aging process affects drug metabolism in three main ways. First, reduced HBF delivers the drug to the liver at a slower rate. Second, the decrease in liver mass influences hepatic function. Finally, the liver's intrinsic metabolic activity is also decreased. Therefore, as less drug reaches the liver per unit time and when it does less is metabolized due to the decrease in its metabolic activity, the duration of action of the drug will be increased.^{4,5} Increasing the percentage of unbound drug will have the same effect as more drug will be available to cause an effect. Foldes and Deery²¹ calculated the protein-bound fraction of atracurium to be ~82%. With decreased hepatic function, less albumin is produced and thus protein binding of atracurium is decreased. When it decreased to 10%, they found the amount of circulating free atracurium increased by 28%,

thus leading to an increase in the duration of action of a given dose.²¹

However, the relative changes and contribution of the above effects are unknown and variable. In addition to the above factors, age, sex, genetics also play a major role in metabolic capacity. Therefore, it is practically impossible to quantify the extent of hepatic function reduction and accurately calculate the necessary drug dosage based on liver function tests.^{4,5}

Excretion

Elimination of many drugs from the body occurs primarily via renal excretion. The half-life of drugs is increased as renal function is reduced. Renal function declines with age. Renal mass may decrease as much as 30% by the age of 80, with the greatest reduction occurring in the renal cortex, corresponding with a decrease in the number of functioning glomeruli. The counter current gradients in the loop of Henle may be disrupted. Moreover, renal blood flow (RBF) decreases by ~10% per decade due to a decrease in size of the renovascular bed. Regional RBF changes occur with decrease in cortical blood flow, whereas medullary blood flow is preserved. As RBF is reduced, glomerular filtration and concentrating ability decline linearly at ~1% per year from 30 to 80 years.¹⁴ Glomerular filtration rate and creatinine clearance decrease with age, but the serum creatinine level remains relatively unchanged because muscle bulk also decreases with age, resulting in less creatinine production.^{4,5}

In contrast to the uncertainty surrounding hepatic influence on pharmacology, the influence of renal changes with age can be predicted with greater certainty. Dose adjustments can be guided by any changes in laboratory measurements (eg, glomerular filtration rate or serum creatinine).

Effect site concentration

Muscle blood flow has been suggested as a factor that influences delivery of drugs to the muscle end plate. Regional blood flows, including the muscle blood flow, are reduced in the elderly. Therefore, a more important concentration gradient between the effect site and the plasma in the elderly patients may exist, which is illustrated by a lower k_{eo} in the elderly.^{4,5,21} The slow onset and longer duration of action of most NMBAs in elderly patients, poorly explained by the modest changes in elimination kinetics, might correspond to this phenomenon.

Pharmacodynamics

Pharmacodynamics describes the effect a drug has on the body. All drugs affect the numerous organ systems in the

body in different ways and cause variable adverse effects depending on their pharmacologic interactions. Aging causes some of these interactions to be more and others to be less pronounced.

In the context of this review, of particular concern is the stimulation of both muscarinic and nicotinic receptors by suxamethonium. Stimulation of cardiac muscarinic receptors in the sinoatrial node may lead to cardiac arrhythmias ranging from bradycardia to nodal rhythms and ventricular tachycardia. Muscle fasciculation and hyperkalemia may be exacerbated in elderly patients with renal failure, leading to intraoperative cardiac events.²² Abdominal muscle fasciculation and an increase in vagal tone may result in a suxamethonium-induced increase in intragastric pressure.²³ However, risk of regurgitation and aspiration is negated by the simultaneous increase in lower esophageal pressure.²³

Use of suxamethonium, particularly after use of anticholinesterase drugs, may result in a Phase II block, and this effect may be markedly prolonged in patients with chronic renal failure,²⁴ which is more common in the elderly.

Nondepolarizing agents have their own complications. The use of benzyliisoquinoliniums, such as atracurium, may result in histamine release, resulting in marked hypotension from tubocurarine and mivacurium.²¹ However, this does not appear to be clinically significant.²⁵

Moreover, cisatracurium has very little, if any, cardiovascular effects, leading Cope and Hunter²⁵ to suggest that it is the most suitable nondepolarizing NMBA for elderly patients.

Pharmacology of NMBAs in the elderly

Clinical findings

Onset time and duration of action

The onset time of NMBAs is usually prolonged in the elderly irrespective of the drug used (vecuronium, rocuronium, suxamethonium, cisatracurium).^{26–30} Studies showing no difference in the onset time of neuromuscular blockade do exist; however, they used 2–3 times the ED₉₅ as their initial dose.³¹ Koscielniak-Nielsen et al²⁸ showed that, compared with younger patients, NMBAs in the elderly produce similar degree of neuromuscular blockade, but after a 2 minute delay.

Depolarizing NMBAs

Suxamethonium

The level of cholinesterase is decreased in the elderly.³² Frail elderly patients have lower plasma cholinesterase activity than fit older patients.⁶ Thus, less hydrolysis of suxamethonium

resulting in longer duration of action is expected when it is administered to elderly patients.

Nondepolarizing NMBAs

Aminosteroids

Muscle relaxants with a steroid structure (pancuronium, vecuronium, rocuronium) are mainly eliminated by the liver through metabolism and biliary excretion, and partially excreted in the urine. They are poorly bound to plasma proteins. These large molecules are highly ionized regardless of pH, which limits their distribution to the extracellular compartment. As a consequence, their Vd remains unchanged or slightly decreases with aging.

Pharmacokinetic parameters for steroid NMBAs are modified by aging, with a trend toward reduction in both clearance (~30%) and distribution volumes (~25%), causing less redistribution of the drugs out of the central compartment. These are the main mechanisms leading to a prolongation of action of aminosteroid NMBAs.^{33,34}

Vecuronium is scarcely metabolized, with 40% excreted unchanged in the bile and 30% in the urine. A limited amount of the drug is deacetylated in the liver with one active metabolite. As both HBF and glomerular filtration rate are reduced with age, vecuronium clearance is decreased by ~30% in this population, without any modification in the Vd. This is probably the main mechanism for the prolongation of duration of action and recovery intervals (up to 30% longer) in elderly patients.^{33,35,36} Simply titrating dose to effect, rather than giving a fixed dose, may avoid this prolongation of recovery time.

Rocuronium is eliminated in a similar manner to vecuronium. Approximately 75% is eliminated in the bile and 10% in the urine. A little rocuronium undergoes deacetylation, and no significantly active metabolites are produced. Clearance of rocuronium decreases with age, almost by 30% when compared with adults in their 40s.²⁹ This explains its prolongation of action after a bolus for intubation or maintenance. After a bolus dose for intubation or maintenance, its action is prolonged.²⁹ This prolongation may be as much as a twofold increase, from 31 minutes in younger patients to 51 minutes in the elderly.³⁷ Therefore, in elderly patients, extra doses should be administered with care, only after the reappearance of train-of-four response.

Clinical effects of some neuromuscular blockers are occasionally not readily explained by pharmacokinetic changes. Doxacurium exhibits a prolonged duration of action similar to other NMBAs despite its clearance and elimination half-life not appearing to alter with age.³⁸ Conversely, despite

reduced clearance of pipecuronium in renal failure,³⁹ there appears to be no clinical reduction in the duration of action in the elderly.⁴⁰

Benzylisoquinoliniums

The currently available benzylisoquinoliniums include atracurium, mivacurium, and cisatracurium. Atracurium and mivacurium are mixtures of stereoisomers with varying potencies and pharmacokinetic properties. Atracurium is a mixture of ten isomers, one of them being cisatracurium.

Like steroid NMBAs, benzylisoquinoliniums are big molecules that do not cross lipid membranes. They are more protein bound than steroid compounds and due to less protein binding in the elderly, their Vd is slightly increased.

Atracurium and cisatracurium are eliminated from the body by Hofmann degradation, a process that is temperature and pH-dependent. Therefore, compared with steroidal NMBAs, they depend less on renal and hepatic function for their elimination.

Metabolism or hydrolysis of benzylisoquinolinium compounds is diverse. Atracurium and cisatracurium mainly undergo spontaneous degradation not only through Hofmann degradation but also secondarily ester hydrolysis. This process accounts for ~83% of cisatracurium elimination but only for ~40% of atracurium total clearance.³⁰ The fraction of atracurium that does not undergo Hofmann elimination is mainly metabolized in the liver and eliminated renally. Renal elimination of atracurium ranges from 10% to 50%, whereas for cisatracurium is ~16%.⁴¹

The pharmacokinetics of atracurium and cisatracurium are altered in the elderly. Parker et al⁴² in 1992 showed that with increasing age, clearance decreases and elimination half-life increases. Specifically, in the case of atracurium, the half-life is increased by 15%.^{43,44} However, these pharmacokinetic changes are not translated to clinically significant effects.^{43,45} In elderly patients, recovery from both induction and maintenance bolus of cisatracurium is increased.^{30,46}

Elderly patients are more sensitive to atracurium doses, the reason for which remains unclear.⁴⁷ Xue et al⁴⁷ showed the above to be true, as smaller doses were needed to produce the same clinical result and the duration of action of a given dose was increased. A proposed mechanism was the increased sensitivity of the neuromuscular junction. However, this might not be the answer as d'Hollander et al³⁵ found that both in the elderly and the younger patients, the same dose of atracurium was needed to suppress the twitch response by 50%.

Another benzyliisoquinolinium, mivacurium, a short-acting NMBA, showed prolongation of recovery and increased onset time.^{27,48} It is almost exclusively eliminated through hydrolysis by plasma cholinesterases,³¹ the activity of which decreases in the elderly.²⁷ Its clearance and elimination half-life in the elderly are thought to be unchanged.⁴⁸ In clinical practice, Dahaba et al⁴⁹ suggested a reduction of infusion dose from 0.5 to 0.4 mg/kg/h after a standard initial dose of 0.15 mg/kg.

Sagir et al⁵⁰ directly compared rocuronium, vecuronium, and cisatracurium in elderly patients undergoing abdominal surgery. They concluded that the benzyliisoquinolinium compound was safer than the two aminosteroids in the elderly because it performed better in time to positive strength and visual disturbance tests, indicating less risk of residual neuromuscular blockade.⁵⁰

Interpatient variability of recovery

Interpatient variability in neuromuscular blockade is more pronounced in the elderly population. Duration of actions of various neuromuscular blockers ranges from cisatracurium (37–81 minutes), vecuronium (35–137 minutes), and rocuronium (33–119 minutes).⁵¹ Cisatracurium has the smallest median variability of duration (7 minutes) compared with vecuronium and rocuronium (18 minutes each).⁵¹ This suggests greater reliability in using cisatracurium for elderly patients.⁵²

A possible reason for the interpatient variability may be the usage of actual body weight in estimating dosages of NMBAs. Variations in body habitus and composition of the body of the elderly may result in an overdosing due to the altered pharmacokinetics of NMBAs caused by, as previously mentioned, increased fat, decreased muscle mass, and lower Vd.³⁷

With suxamethonium, the decrease in the level of plasma cholinesterase would result in a more prolonged duration of action. This level of plasma cholinesterase may also depend on the physical fitness of the elderly patient, with frail elderly patients having more impaired enzyme activity.

Steroid neuromuscular blockers appear to have a greater degree of variability as they are dependent on organ elimination. Furuya et al³⁷ showed that the time of appearance of the first post-tetanic count was both increased and more variable in patients over 70 years compared with younger patients.

Furthermore, it appears that the usage of volatile anesthesia may produce increased variability in the duration of action of steroidal NMBAs compared with cisatracurium in the elderly. A comparison of Furuya et al's³⁷ study using sevoflurane with Baykara's study using propofol and opioid

showed an increase of 19 minutes with sevoflurane.⁵³ This increase is thought to be due to sevoflurane pharmacodynamically potentiating the neuromuscular blocker as well as the volatile anesthetic, limiting peripheral blood flow to the muscles.³⁷

Use of neuromuscular blockade monitoring in the elderly

The increased duration of action and decreased clearance of most NMBAs may predispose geriatric patients to inadequate recovery from neuromuscular blockade. Advanced age is a risk factor for residual neuromuscular block and resulting respiratory complications.⁹ Because of the above, it is even more important in elderly patients to monitor the effects of the NMBAs both in determining the frequency and dosage of repeated administration of these agents and the appropriate administration of reversals.

Quantitative monitors for monitoring residual blockage are not commonplace, with an estimated 10% of anesthesiologists using them routinely.^{25,54} There is also no unanimous means of confirming complete recovery from neuromuscular blockade.^{25,54}

There are different modes of nerve stimulation (eg, single twitch, double-burst stimulation, train-of-four stimulation, and tetanic stimulation and posttetanic count) and although commonly used, visual assessment can be inaccurate as a means of monitoring depth of neuromuscular blockade, mechanical or electrical methods being preferable. Mechanomyography, frequently using the adductor pollicis of the thumb, may be cumbersome and is perhaps better viewed as a research tool; it is generally impractical for use in the operating theatre.⁵⁵ Electromyography (recording the compound action potential generated by the muscle contraction) and acceleromyography (measuring acceleration rather than force of contraction) are both electrical methods that are less bulky. Kinemyography also shows promise, using piezoelectric crystals as motion sensors.⁵⁶

Of the various tests available, the train-of-four (TOF) stimulation appears to be the most commonly used, and some papers advocate a TOF >0.9 as sufficient recovery of neuromuscular blockade to avoid related postoperative complications.^{57–59} However, other studies suggested that even a TOF >0.9 shows insufficient recovery of neuromuscular blockade.^{60,61} Therefore, it is recommended that a combination of TOF assessment together with clinical tests (eg, sustained head lift or grip strength) should be used for the assessment of neuromuscular recovery.⁵⁰

Neuromuscular blockade reversal in the elderly

A recent study by Murphy et al⁶² suggested that postoperative residual neuromuscular blockade may be twice as common in the elderly (incidence of 57%) as in the younger population (30%), leading to increased postanesthesia care unit and hospital stay as well as a higher incidence of hypoxemic events, airway obstruction, and other symptoms of muscle weakness. This illustrates the need for accurate dosage of NMBA, vigilant monitoring of their effects, and if necessary, appropriate administration of reversal agents.

Reversal of neuromuscular blockade, if required, tends to be with anticholinesterase drugs. Neostigmine, pyridostigmine, and edrophonium are all acetylcholinesterase inhibitors but have different uses.

Neostigmine is the most common anticholinesterase drug used, antagonizing the effects of neuromuscular blockers by carbamylation of their esterase sites. Neostigmine's Vd is increased in the elderly as it is a polar molecule that is not very lipid soluble and, as previously mentioned, the body's fat content increases compared to muscle, resulting in a more prolonged duration of action.⁶³ Similar to neostigmine, pyridostigmine's action is prolonged in the elderly due to decreased renal function leading to decreased plasma clearance.⁶⁴ In contrast, the duration of action of edrophonium remains unchanged. Therefore, neostigmine and pyridostigmine are preferable to edrophonium as NMBA reversal agents as their prolonged duration of action can negate the prolonged duration of action of NMBA that occur with advancing age.⁶³

Sugammadex, a modified γ -cyclodextrin, reverses the neuromuscular blockade of aminosteroidal agents, such as rocuronium and vecuronium, by binding and forming a complex, which is primarily excreted by the kidneys. Therefore, a reduction in kidney function would lead to decrease in clearance and extension of its half-life and duration of action.⁶⁵ In patients older than 75 years, a reduction of clearance to 50% would result in a near doubling of the effective half-life of sugammadex.⁶⁵ Reversal lasts significantly longer in elderly patients.⁶⁰ Suzuki et al⁶⁶ speculated that this was due to, first, decreased cardiac output and, second, decreased muscle blood flow. Another group quantified the increase in duration by finding that neuromuscular blockade lasted 0.7 minutes more in the elderly patients compared with younger adults.⁶⁵ This finding was confirmed by Kadoi et al,⁶⁷ who found significant differences in both recovery of TOF ratio to >0.9 and time to first spontaneous breath between the younger (<50 years)

group (403 s) and the elderly (>70 years) group (443 s). Of note are the recommendations from the manufacturers of sugammadex that, although the recovery time tends to be slower, the same dose recommendation as for younger adults should be followed to minimize the risk of any residual neuromuscular blockade.⁶⁸

Conclusion

This article provides a review for anesthetists to consider modifications in the administration of neuromuscular blockers for the elderly patient undergoing general anesthesia. Although the main focus has been on age-related changes, it is stressed that by virtue of aging, other factors also come into play, notably cardiovascular or renal and hepatic disease, which independently influence the distribution and handling of drugs. Furthermore, there is increasing recognition of obesity in the aging population, which in turn can influence drug disposition.^{69,70} There must be careful deliberation of pharmacokinetic and pharmacodynamic principles on an individual case basis to avoid unintentional prolonged duration of action. Consideration of appropriate agents and the usage of neuromuscular blockade monitoring as well as the judicious use of NMBA reversal agents would decrease the risk of residual blockade and postoperative complications.

Disclosure

The authors report no conflicts of interest in this work.

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