Nondepolarizing Neuromuscular Blocking Agents in the Elderly: Dosing Paradigms Revisited

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Introduction

Estimates are that by the year 2050, the percentage of people in the United States aged 65 and older will increase from 13% to almost 21%. Translating this into the actual number of people aged 65 and older means that while in 2000 there were 35 million people in this demographic, there will be 54.6 million in 2020 and 86.7 million in 2050. Percentage-wise more geriatric patients than young adults require surgical procedures. Most anesthesiologists provide care for geriatric patients currently and more will likely be needed to do so in the future.

Muscle relaxation is only one of the four components of a general anesthetic. Whether this should be provided through deep anesthesia, with either volatile anesthetics or intravenous anesthetics, or with nondepolarizing neuromuscular blocking agents can be debated. Certainly there are advantages and disadvantages to both techniques. When, however, it is provided through pharmacologic compounds specifically designed to provide relaxation, attention must be paid to dosing and redosing of the compound as residual neuromuscular block is very much a risk of administering these agents and puts patients at increased risk of postoperative pulmonary complications (Berg et al., 1997; Murphy et al., 2008). Special consideration should be given to their use in the geriatric patient because physiologic changes that accompany aging, including decreases in hepatic and renal blood flow and function, may impact the pharmacodynamics and pharmacokinetics of these nondepolarizing neuromuscular blocking agents.

The Aged Neuromuscular Junction

Aging is accompanied by several physiologic and anatomic changes (Table 1). Among these are a reduction in the number of motor neurons in the spinal cord (Tomlinson & Irving, 1977) and loss of muscle fibers (Lexell, Taylor, & Sjostrom, 1988). This is accompanied by a decrease in the size of type 2 muscle fibers (Lexell et al., 1988). In spite of these changes, an augmented twitch response is obtained by stimulating a motor nerve (Doherty & Brown, 1997) because of an increase in the size of the motor unit. In addition to an increase in size, there are also changes within the motor unit. The number of preterminal axons is increased as is the distance between the preterminal axon and the motor end plate. Additionally, the folds of the motor endplate at the neuromuscular junction are flattened (Frolkis, Martynenko, & Zamostyan, 1976). Changes with advancing age extend beyond the motor end plate. Ongoing denervation leads to proliferation of extrajunctional receptors in the elderly (Oda, 1984). In a rat model, the acetylcholine concentration in a motor nerve terminal is lower than that found in younger animals. However, release of acetylcholine release is increased because of an increased number of nerve terminals per motor end plate (Frolkis et al., 1976).

What is the significance of these changes? Is there resistance to neuromuscular blockers because of the proliferation of extra-junctional receptors as seen in disuse atrophy or is there increased sensitivity to nondepolarizing blockers because of the

decreased release of acetylcholine from prejunctional neurons and greater distance between the pre and post-terminal components of the neuromuscular junction? Interestingly, differences in the dynamics of the neuromuscular blockers do not appear to be due to changes in the neuromuscular junction. The ED_{95}, or dose of relaxant causing 95% neuromuscular block, is, as shown in Table 2, similar the elderly and young patients. Many investigators have shown that when elderly patients have the same plasma concentration of neuromuscular blocker as do young adults, they also have the same degree of neuromuscular block (Duvaldestin, Saada, Berger, D'Hollander, & Desmonts, 1982; Matteo et al., 1985; Rupp, Castagnoli, Fisher, & Miller, 1987). Differences in dynamic behavior, therefore, appear to be due to differences in pharmacokinetics of the compounds in the aged patient population.

Onset of Neuromuscular Block

Differences in onset are ideally studied using doses that do not cause complete paralysis so that the time required to achieve maximal effect can be quantified. In doses that cause complete paralysis, such as 2 or 3x ED_{95}, the maximal effect that can be measured is 100% neuromuscular block. Peak effect, however, may occur at some point following maximal neuromuscular block. A study of vecuronium, 0.03 mg/kg, clearly delineated differences in the time to maximal effect in pediatric, young adult and elderly patients (Koscielniak-Nielsen et al., 1993). In this study, the geriatric patients had an onset time that was almost 2 minutes slower than that in young adults – in spite of both groups developing similar degrees of maximal neuromuscular blockade.

To exert their effect, nondepolarizing neuromuscular blocking agents need to be carried to their site of action, the neuromuscular junction. There are different factors that influence the rate at which this is done including cardiac output, circulation time and muscle blood flow (Donati, 1988). Although not all investigators have found a slower onset of effect in geriatric patients following administration of doses as large as, and larger than, the ED_{95}, many have (Table 3). The greater time required for complete paralysis may not be completely attributable to a decreased cardiac output as physically active, healthy geriatric patients do not have a decline in cardiac function (Rodeheffer et al., 1984). Pharmacodynamic modeling has demonstrated that geriatric patients have a slower biophase equilibration and this may be an additional reason for a slower onset of maximal effect (Sorooshian et al., 1996).

Physicians overdose medications – muscle relaxants being among those overdosed. A recent study of a computerized order entry system demonstrated that physicians selected doses that were larger than those recommended more than 70% of the time. Use of a computerized system, that provided recommended dose ranges, only minimally reduced this practice (Peterson et al., 2007). Overdose of depolarizing and nondepolarizing muscle relaxants is not uncommon and is frequently intentional. Typically doses of nondepolarizing neuromuscular blocking agents larger than their ED_{95} are used to facilitate endotracheal intubation in order to speed the onset of block (Table 4). Increasing the multiples of the ED_{95} of gantacurium, a new short-acting muscle relaxant, or rocuronium administered above 1x ED_{95} will shorten onset of 100% block by approximately 1 minute (Magorian, Flannery, & Miller, 1993) (Belmont et al., 2004). There is a limit, though, to the degree to which onset can be shortened (Belmont et al., 2004), even in young adults, and, with the exception of rocuronium, no compound has an

onset of effect that approaches that of succinylcholine. This, coupled with the slower onset of neuromuscular block in the elderly (Table 3), may lead clinicians to administer even larger doses of neuromuscular blocking agents in an attempt to further shorten onset of effect. Overdosing nondepolarizing neuromuscular blocking agents exposes patients to an increased risk of the side effects of the compound, such as histamine release or vagolysis, as well as an increased duration of action (Magorian et al., 1993). For compounds that are eliminated through the kidney or the liver, recovery of neuromuscular function occurs as the drug is redistributed from the neuromuscular junction to storage sites. With administration of larger or repeated doses, recovery increasingly occurs during the elimination phase, rather than the redistribution phase, and is increasingly prolonged (Wright et al., 1994).

Elimination and Metabolism of Nondepolarizing Neuromuscular Blocking Agents

Aging is accompanied by decreases in hepatic and renal blood flow and function. As indicated in table 5, all relaxants used clinically over the past 25 years have some component of elimination through either the liver or the kidney. Even for those that don't, a decrease in hepatic or renal function can lead to decreased butyrylcholinesterase levels and, for that reason, a prolonged duration of action.

Pharmacokinetics and Pharmacodynamics of Neuromuscular Blocking Agents

With the exception of pipecuronium, all of the long-acting neuromuscular blocking agents have a prolonged duration of effect in geriatric patients. For pancuronium, metocurine and d-tubocurarine, this prolonged effect is attributable to a decreased clearance and a prolonged elimination half-life (Duvaldestin et al., 1982; Matteo et al., 1985; McLeod, Hull, & Watson, 1979). A pharmacokinetic explanation for the prolongation of effect of doxacurium in the elderly is not as readily available. Its clearance is the same in both the young and the aged (Dresner et al., 1990) and its elimination half-life is not significantly increased. Its volume of distribution in the elderly, however, is significantly increased (Dresner et al., 1990). In the one study directly comparing the kinetics and dynamics of pipecuronium in the elderly (Ornstein, Matteo, Schwartz, Jamdar, & Diaz, 1992), there was no difference in duration of action after bolus administration, clearance, elimination half-life or volume of distribution. This is surprising in light of reports of decreased clearance of this compound in patients with renal dysfunction (Caldwell et al., 1989) but is consistent with the report that this compound can be used in the elderly without dosing adjustment (Azad et al., 1989).

The intermediate-acting muscle relaxants depend less on the kidney and the liver for their elimination from the body. Never-the-less, durations of action and pharmacokinetics are impacted by advanced age. In the case of the steroidal intermediate-acting muscle relaxants, the duration of action of action of vecuronium and rocuronium is dependent on study design. Recovery of neuromuscular function following administration of these compounds occurs during redistribution of the relaxant out of the central volume rather than during elimination (Wright et al., 1994). D'Hollander (A. d'Hollander, Massaux, Nevelsteen, & Agoston, 1982), McCarthy (McCarthy et al., 1992) and Lien (Lien, Matteo, Ornstein, Schwartz, & Diaz, 1991) found the duration of action and recovery intervals of vecuronium to be significantly prolonged in elderly patients. This prolonged duration of action is most likely due to the decreased clearance of vecuronium

(Lien et al., 1991) (Rupp et al., 1987) in geriatric patients compared to younger adults. When vecuronium is titrated to effect, though, rather than administered as a fixed bolus dose, recovery intervals are not prolonged (Rupp et al., 1987).

Like vecuronium, rocuronium also has a prolonged duration of effect in geriatric patients when administered as a bolus, whether for intubation or as a maintenance dose. (Bevan et al., 1993) (Matteo, Ornstein, Schwartz, Ostapkovich, & Stone, 1993) (Baykara, Solak, & Toker, 2003). In the elderly, clearance of rocuronium is decreased by almost 30% when compared to young adults (Matteo et al., 1993) explaining its prolongation of action in this patient population.

Atracurium and cisatracurium, one of the stereoisomers comprising atracurium, depend less on either the kidney or the liver for their elimination from the plasma than do the intermediate-acting steroidal neuromuscular blocking agents. Both are eliminated primarily through Hofmann degradation – a base and temperature catalyzed process. As a result of its elimination, when incubated in buffered saline at a pH of 7.4 at a temperature of 37ºC, atracurium has a half-life life of one hour (Tsui, Graham, & Torda, 1987). In human plasma, this is decreased by up to 65% (Stiller, Cook, & Chakravorti, 1985).

The kinetics of atracurium and cisatracurium, however, do appear to be influenced by advanced age. The elimination half-life of atracurium is prolonged by 15% in elderly patients. (Kitts et al., 1990) (Kent, Parker, & Hunter, 1989) and its volume of distribution is larger. In another study of the pharmacokinetics of atracurium in the elderly, clearance was found to be decreased and elimination half-life increased (Parker, Hunter, & Snowdon, 1992). These pharmacokinetic changes do not, though, translate into a prolonged duration of effect in this patient population when compared to younger adults (Kitts et al., 1990) (A. A. d'Hollander, Luyckx, Barvais, & De Ville, 1983).

While the extent of renal elimination of atracurium has been found to range from 10 – 50%, that of cisatracurium is 16% (Kisor et al., 1996). Although the elimination half-life of cisatracurium is increased in the elderly, as is its volume of distribution, its clearance is the same as it is in young adults (Ornstein et al., 1996; Sorooshian et al., 1996). Neither recovery from bolus administration of 2 to 3 times the ED_{95} of cisatracurium nor maintenance doses of 0.03 mg/kg is prolonged in elderly patients (Ornstein et al., 1996; Puhringer et al., 2002; Sorooshian et al., 1996).

Mivacurium is unique in that it is the only available nondepolarizing neuromuscular blocking agent with a short duration of action and in that it is almost exclusively eliminated through butyrylcholinesterase mediated hydrolysis (Lien et al., 1994). That being said, advanced age is associated with decreased butyrylcholinesterase activity (Maddineni, Mirakhur, & McCoy, 1994). While recovery from mivacurium-induced block is prolonged in the elderly (Maddineni, Mirakhur, McCoy, & Sharpe, 1994; Ostergaard, Viby-Mogensen, Pedersen, Holm, & Skovgaard, 2002), the clearance and elimination half-life of mivacurium in the elderly are unchanged (Ostergaard et al., 2002). The finding that elderly patients require a lower infusion rate to maintain a stable depth of block (Goudsouzian et al., 1997) is consistent with reports that the mivacurium infusion rate required to maintain a stable depth of block is dependent on patient butyrylcholinesterase activity (Hart, McCarthy, Brown, Lau, & Fisher, 1995) - which is decreased in geriatric patients (Maddineni, Mirakhur, & McCoy, 1994).

Inter-patient Variability of Recovery

Ensuring complete recovery of neuromuscular function is important as inadequate recovery of neuromuscular function is associated with an increased incidence of critical respiratory events (Murphy et al., 2008). Geriatric patients are at risk for inadequate recovery since duration of action is increased and clearance of the relaxant is decreased for the majority of clinically available compounds. In a study published 12 years ago, advanced age was one of the factors associated with residual neuromuscular block and respiratory complications (Berg et al., 1997). Anticipating recovery from either an intubating or a maintenance dose of relaxant is important in determining whether to redose the relaxant or whether or not anticholinesterase can be administered. There is substantial variability in spontaneous recovery from nondepolarizing neuromuscular blocking agents and this is most pronounced with the steroidal compounds (Claudius, Garvey, & Viby-Mogensen, 2009). Inter-patient variability has been observed in elderly, as well as in young, adults (Puhringer et al., 2002). Additionally, the degree of variability in response to nondepolarizing neuromuscular blocking agents appears to be more marked in the geriatric population (Puhringer et al., 2002) (Arain, Kern, Ficke, & Ebert, 2005).

Monitoring

Nondepolarizing neuromuscular blocking agents should never be administered without using a monitor of neuromuscular block to determine the effect of administered relaxants – especially in the elderly. Quantitative monitors are optimal for monitoring residual neuromuscular block and their use should be routine (Eriksson, 2003). They are not, however, commonly available and, in their absence, use of the train-of-four count has been shown to effectively guide decisions in redosing relaxants and administration of anticholinesterases (Kopman, Zank, Ng, & Neuman, 2004). Use of the train-of-four count in response to train-of-four monitoring may decrease the incidence of critical episodes of postoperative weakness even when agents with a long duration of action are used (Kopman, Ng, Zank, Neuman, & Yee, 1996).

Conclusions

In dosing neuromuscular blocking agents in geriatric patients there are a few guiding principles that should be followed. Doses should not be larger, for either intubation or maintenance of block, than is recommended for young adults. Dosing intervals should not be more frequent than used in younger patients. The depth of block obtained in response to a neuromuscular blocking agent should be monitored. A prolonged duration of effect of the neuromuscular blocking agent should be anticipated. Altered pharmacokinetics and pharmacodynamics of these compounds in the elderly patient requires that clinicians consider the impact of neuromuscular blocking agents each time a dose is administered….and that the dose administered be carefully chosen.

Table 1

Changes in the Neuromuscular Junction with Advancing Age
Decrease in the number of motor units
Lengthening of the of motor unit
Decreased number of preterminal axons
Increased number of nicotinic receptors per motor unit
Proliferation of extrajunctional receptors
Decreased amount of acetylcholine in each motor neuron
Increased distance between the preterminal axon and the motor end plate
Flattening of the folds of the motor end plate
Decreased amount of acetylcholine released in response to stimulation

Table 2

Neuromuscular Blocking Agent	ED95 (mg/kg) in Young Adults	ED95 (mg/kg) in Geriatric Patients	Reference
Pancuronium	.078	.081	Duvaldestin et al., 1982
Doxacurium	.029	.026	Koscielniak-Nielsen et al., 1992
Vecuronium	.041	.038	(O'Hara, Fragen, & Shanks, 1985)
Rocuronium	.521	.369	Bevan et al., 1993
Mivacurium	0.053	0.061	Ostergaard et al., 2002

Table 3

NMBA	Dose (mg/kg)	Onset (minutes)		Reference
		Elderly adults	Young adults	
Mivacurium	0.15	2.0	2.1	Maddineni, Mirakhur, McCoy et al., 1994
Vecuronium	0.1	4.9	3.7	Koscielniak-Nielsen et al., 1993
	0.1	3.5	2.6	Kitajima, Ishii, & Ogata, 1995
	0.12	2.1	1.6	McCarthy et al., 1992
Rocuronium	0.6	4.5	4.1	Matteo et al., 1993
	1.0	1.3	1.0	Bevan et al., 1993
Cisatracurium	0.1	4.0	3.0	Sorooshian et al., 1996
	0.1	3.4	2.5	Ornstein et al., 1996
Pipecuronium	0.07	6.9	4.5	Ornstein et al., 1992
Doxacurium	0.025	11.2	7.7	Dresner et al., 1990

Table 4

Neuromuscular Blocking Agent	ED95 (mg/kg)	Multiples of the ED95 used for intubation
Pancuronium	0.07	1 – 1.3
Pipecuronium	0.04	1.5 - 2
d-Tubocurarine	0.50	1
Metocurine	0.30	1 – 1.3
Doxacurium	0.025	2 - 3
Rocuronium	0.30	2 - 4
Vecuronium	0.04	2
Atracurium	0.25	2– 2.5
Cisatracurium	0.04	3 - 4
Mivacurium	0.08	2.5 - 3

Table 5

Neuromuscular Blocking Agent	Means of Elimination		
	Kidney	Liver	Other
Pancuronium	+++++	+	--
Pipecuronium	+++++	+	--
Doxacurium	+++++	+	--
d-Tubocurarine	++++	++	--
Metocurine	+++++	+	--
Vecuronium	++	++	--
Rocuronium	+	+++	--
Atracurium	+	--	+++++
Cisatracurium	+	--	++++
Mivacurium	+/-	--	+++++

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