Pharmacologic Considerations of Anesthetic Agents in Geriatric Patients

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KEYWORDS
- Geriatric anesthesia • Induction dosing • Pharmacokinetics
- Postoperative cognitive dysfunction (POCD) • Elderly • Aging

KEY POINTS
- Perioperative physicians should be aware of the physiologic changes with aging to avoid overdose and risk of toxicity.
- Perioperative physicians must be vigilant to the development of postoperative cognitive delirium and judiciously administer anesthetic agents in the perioperative period.
- Perioperative physicians should use a tailored approach to the anesthetic dosing of drugs because of the heterogeneity of the geriatric population.

PHARMACOLOGIC CONSIDERATIONS OF ANESTHETIC AGENTS IN GERIATRIC PATIENTS

Vigilant perioperative physicians must be cognizant of the aging population presenting for anesthetic care. Because of an increase in life expectancy coupled with improved treatments for chronic disease states, the elderly population is increasing. By 2030, 20% of the population will be older than 65 years; by 2050, 31 million citizens will be more than 80 years old.1 Because elderly patients are 4 times more likely to undergo surgery than their younger counterparts, more procedures requiring anesthetics will result.2,3

Significant concerns for anesthesiologists include the development of delirium and postoperative cognitive dysfunction (POCD).4,5 POCD and delirium are always risks in geriatric patients in the perioperative period, which mandates careful assessment of

Disclosure: The authors have nothing to disclose.

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anesthetic choices and an appreciation of the pharmacokinetics and pharmacodynamics of agents.6,7

Physiologic changes present in the aging population versus younger patients require perioperative physicians to be aware of the nuances of anesthetic drugs in an effort to provide an effective and structured approach to the management of geriatric patients. Age alters the pharmacokinetic and pharmacodynamic aspects of anesthetic management. The functional capacity of organs declines and coexisting diseases further contribute to physiologic decline. Awareness of age-related changes by anesthesiologists is of particular importance because of the presence of polypharmacy in elderly patients.8 Because of the multiple drugs, which may act synergistically or at cross-purposes, the risk of adverse effects is heightened in the elderly population. It is estimated that more than 90% of persons more than 65 years of age use at least 1 drug, 40% take 5 or more drugs per week, and 12% use 10 or more drugs per week.9,10 As a result of the potential for multiple drug interactions, a careful titration of drugs in the perioperative setting is mandated.

PHYSIOLOGIC CHANGES IN GERIATRICS

Geriatric patients share more in common with the pediatric population than younger adults because of the physiologic changes that occur in the life cycle. In general, aging is characterized by decreased reserve in organ structure and function with an increase in disorders and a decrease in homeostatic mechanisms for combating illnesses.11 However, there is no such concept as the typical geriatric patient. This heterogeneity mandates that anesthesiologists determine where an elderly patient is on the spectrum of remarkably fit to critically ill. The changes occurring as a result of aging affect every organ system and deserve consideration (Table 1).

<table>
<thead>
<tr>
<th>Organ System</th>
<th>Effect</th>
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| Body composition | Increased total body water: increased initial plasma volumes for bolus doses  
Reduced lean mass: reduced Vd of hydrophilic drugs  
Increased adipose tissue: increased Vd for lipophilic drugs and prolonged elimination |
| Renal | Decreased function  
Decreased renal blood flow  
Reduced clearance/higher serum drug levels |
| Hepatic | Decreased function/blood flow  
Decreased phase I (P450 enzyme) reactions  
Increased drug levels |
| Neurologic | Cognitive decline  
Decreased nerve conduction velocity  
Increased sensitivity to sedatives, hypnotics, opioids |
| Cardiac | Reduced cardiac output  
Increased systemic vascular resistance  
Reduced beta-receptor responsiveness |

Abbreviation: Vd, volume of distribution.
Body Compositional Changes

Geriatric patients develop a loss in muscle mass with an increase in adipose tissue.\textsuperscript{12,13} As a result, patients show an alteration in the volume of distribution (Vd) of anesthetic agents. The decline in muscle mass may not be readily evident because patients may have a normal creatinine value on laboratory results because of alterations in renal structure and function.\textsuperscript{14} In contrast, there is a 20% to 40% increase in body fat with aging, which causes lipophilic agents to have a higher Vd. The net pharmacologic effect is prolonged drug action with fat-soluble agents (intravenous anesthetics).

Importantly, elderly patients also have a reduction in total body water. By age 75 years there is a 20% to 30% decline in both plasma volume and intracellular volume. The pharmacokinetic consequence of this change is a reduction in the central compartment in addition to a significant decrease in the central Vd. The net effect is a higher peak serum concentration after a bolus administration of a drug. Also, for hydrophilic agents, the plasma concentration of the agent is higher in the elderly population than in younger patients.\textsuperscript{15}

The increased initial concentration from a bolus dose causes predictable, undesirable clinical effects. When induction doses are not reduced, exaggerated and prolonged hypotensive responses should be expected, especially with propofol.\textsuperscript{16} Furthermore, increased initial drug levels in the central compartment, when coupled with increased circulation times from reduced myocardial performance, increase the likelihood of greater drug sensitivity and risk of toxicity.

Neurologic Structural and Functional Changes

Neurologically, there is a decrease in cerebral volume, oxygen consumption, blood flow, and blood-brain barrier permeability with aging. Losses occur in both gray and white matter, amounting to an almost 30% loss of brain mass by 80 years of age versus younger patients.\textsuperscript{17} Findings suggest that, after 40 years, the volume and weight of the brain decline by nearly 5% per decade, and the losses accelerate once the brain reaches 70 years of age. Gender also plays a role: cerebral atrophy in men starts earlier, but develops more rapidly in women.\textsuperscript{18}

The neuraxial space is also altered, with a reduction in cerebrospinal fluid volume, a decrease in the size of the epidural space, and an increase in dural permeability. Myelinated nerves have less myelin and also are decreased in quantity in dorsal and ventral nerve roots.\textsuperscript{3,17,19} The net result of these changes is a decreased requirement for intravenous agents and local anesthetics, along with a lesser concentration of volatile anesthetic to achieve a desired clinical effect.

Neural processes and neurotransmitter quantity are decreased in the aging brain. In the cortex, acetylcholine receptors, serotonin receptors, and dopamine receptors decline in numbers and function with age.\textsuperscript{17} In addition, cellular Ca\textsuperscript{2+} levels are altered, leading to decreased function at neuronal synapses via alteration of Ca\textsuperscript{2+} channel activity.

Other receptor changes with aging directly affect the administration of anesthetic agents. Changes in gamma-aminobutyric acid (GABA) receptor activity affect the actions of propofol, etomidate, and benzodiazepines. A decreased presynaptic release of GABA leads to a possible increased response by the elderly to benzodiazepines.\textsuperscript{16} N-Methyl-D-aspartate receptors (NMDA), involved in nociception and memory and learning, are hypofunctional with advancing age, leading to the risk of Alzheimer disease and neurodegeneration.\textsuperscript{20} NMDA antagonists such as ketamine and dextromethorphan have the potential for altered effects in the elderly.
Nociception is altered because of the neurotransmitter and receptor changes; additionally, altered blood flow and nervous tissue damage from hyperglycemia present in the diabetic state may lead to alterations in nociception.\textsuperscript{21}

**Myocardial Structural and Functional Changes**

Myocardial and vascular structure and function are altered in the elderly. Age-related changes begin as early as the fourth decade.\textsuperscript{22} Progressive stiffening of the myocardium and vascular beds occurs primarily from cessation of elastin production, as damaged elastin is replaced by less flexible collagen.\textsuperscript{22} There is a decrease in myocyte number and the development of concentric left ventricular hypertrophy. Functionally, these changes translate to decreased contractility, relaxation, and increased filling pressures, which are characteristic of diastolic dysfunction.\textsuperscript{23} Increases in arterial and venous stiffness from age-related atherosclerosis, fibrosis, and calcification further contribute to myocardial hypertrophy and diastolic dysfunction. For these reasons, diastolic dysfunction is far more common than was previously appreciated, and is present in nearly one-third of elderly patients.\textsuperscript{24}

In parallel, the autonomic nervous system is altered with aging. There is a decrease in parasympathetic function (ie, vagal tone) and an increase in sympathetic nervous system (SNS) activity. The increase in SNS activity is shown by increased circulating levels of norepinephrine coupled with decreased catecholamine uptake at nerve endings.\textsuperscript{22} The natural consequence of increased SNS activity and vascular stiffness is the expected increase in systemic vascular resistance that is commonly seen with advancing age.

Myocardial performance is further affected by age-related alterations in the beta-adrenergic receptor activity.\textsuperscript{22} The decline in beta-adrenergic responsiveness has several important consequences: reduced maximal attainable heart rate (chronotropy) during periods of stress and exercise (a beta-1 effect), poorer vascular relaxation (lusitropy) with direct stimulation (a beta-2 effect), and decreased myocardial contractile responsiveness (inotropy) and ejection fraction.\textsuperscript{25} In order to meet the demands for the increased cardiac output, the aging (less compliant) myocardium relies heavily on adequate preload (intravascular volume and venous capacitance), afterload (arterial tone), and a normal sinus rhythm (atrial kick). Imbalances in these factors result in the aging myocardium being far more susceptible to failure.

Aging also degrades the myocardial conduction pathways, predisposing even the healthiest elderly patients to cardiac arrhythmias. Brady arrhythmias, heart block, and ectopic impulses coexist with beta-receptor, vascular, and diastolic dysfunction.\textsuperscript{26}

Collectively, these alterations in beta-receptor/baroreceptor responsiveness, conduction pathway patency, myocardial relaxation, and vascular stiffness cause the blood pressure lability and orthostasis that are commonly seen in the elderly. Concomitant medications, the hypovolemic state, and anesthetic agents amplify these cardiac changes and vulnerabilities. In addition, a low cardiac output, as seen in the elderly, leads to a higher initial peak concentration because the drug is present in a smaller blood volume during injection, with a greater time to reach the target site of effect. Reduced levels of induction agents are required in the elderly, with a slower onset of action compared with younger patients.

**Pulmonary**

Age-related changes in the lungs and in pulmonary function occur after the third decade.\textsuperscript{27} Because pulmonary complications account for nearly 40% of the postoperative deaths in patients more than 65 years of age, awareness of these changes
is crucial. The development of arthritis, kyphoscoliosis, and osteoporosis creates a less compliant thoracic cage. This stiffer chest wall increases reliance on diaphragmatic breathing, despite declining diaphragmatic strength and endurance. Faltering muscle strength and tone compromise airway protective reflexes, increasing the risk of aspiration.

Aging lung parenchyma loses elastin fibers, causing loss of elastic recoil, and altered lung volumes and capacities. This change may begin as early as the fourth decade, but naturally occurs after the fifth decade. By the seventh decade, air spaces enlarge and reduce the functional alveolar surface area by 50%, causing increased compliance and functional emphysema. These changes alter diffusing capacity and create V/Q mismatch, shunt, and an increased A-a gradient. Chemo-receptor sensitivity is reduced 50% in response to hypoxia and hypercarbia.

At baseline, elderly patients are noted to have lower tidal volumes and higher respiratory rates, to compensate for poorer gas exchange. Taken together, all these pulmonary changes in structure, function, and mechanics predispose geriatric patients to respiratory fatigue, hypoxia, aspiration, and respiratory failure. For this reason, care must be taken to monitor for any signs of residual weakness from incompletely reversed neuromuscular blockade or sedative medications.

Renal
Changes in the renal system play a noticeable role in the metabolism and elimination of agents. Structurally, there is a 25% reduction in renal cortical mass by age 80 years, along with a decrease in renal blood flow by 10% per decade after age 40 years. Further reductions in age-related renal blood flow from long-standing hypertension or diabetes predispose the aging kidney to renal dysfunction. By age 80 years, there is also a predictable 50% decrease in glomerular filtration rate (GFR), from 125 mL/min to 60 mL/min. Consequently, agents that depend on renal elimination have longer systemic half-lives and increased drug levels.

Aging causes reduced renin-angiotensin function and antidiuretic hormone production, predisposing the elderly to altered volume status. As mentioned previously, serum creatinine levels are a poor predictor of renal function in older adults. The GFR is the most useful value to gauge renal function.

Hepatic
Hepatic mass and blood flow decrease with aging. Liver blood flow declines 10% per decade and liver mass decreases by 35%. The liver normally processes drugs via phase I and phase II reactions. Phase I reactions involve the action of the cytochrome P450 system and are slowed down by age and affected by polypharmacy. Drugs cleared by this mechanism are said to be flow limited and have a reduction in clearance of 30% to 40%, in parallel with the changes in hepatic blood flow. Phase II involves the conjugation pathways, which are not affected by age. Drugs cleared primarily through this pathway are said to be capacity limited and, despite changes in hepatic mass, their clearance is well preserved, in the absence of disease, because of the presence of normal hepatic reserve.

Protein binding
Proteins present in the plasma affect the free fraction of protein-bound drugs (most intravenous anesthetic drugs). The circulating free fraction of a drug and the free drug concentration are inversely related to plasma protein levels. Geriatric patients have lower concentrations of albumin (binds acidic drugs) because of age-related declines in production and theoretic nutritional deficits. In contrast, levels of alpha-1 acid glycoprotein, which binds basic drugs, increase only slightly with age. The clinical
relevance of this effect on pharmacodynamics is not entirely predictable, and it has been suggested that it does not seem to have an important impact on geriatric anesthetic pharmacology.33 Plasma cholinesterase (ie, butyl cholinesterase), involved in the metabolism of succinylcholine, has decreased levels in the elderly and affects dosing of this agent.

**Gastrointestinal factors**

Elderly patients have increased gastric pH and also a prolonged gastric emptying time.

As a result of the physiologic changes, the geriatric patient population is at risk for overdose of agents in the perioperative period.

**Pharmacokinetics/pharmacodynamics in geriatrics**

In order to gain an understanding of the actions and elimination of agents in elderly patients, a brief review of pharmacologic concepts is important. The central compartment (designated as V1) is the compartment into which an agent is administered. Depending on the models being used for a particular agent, there may be 2 to 3 compartments assessed to determine pharmacokinetics. Subsequent concentrations depend on distribution and metabolism of agents into and out of the rapidly redistributed vessel-rich compartment (V2) and the vessel-poor region (V3). The total Vd is the sum of the individual compartments. Although beyond the scope of the present discussion, to evaluate the Vd of an agent, the compartment volume, redistribution, and metabolic rate constants must be considered.

**Agent-specific Considerations**

**Induction agents**

**Propofol**

Propofol is the most commonly used induction agent. When administering this agent to elderly patients, dosage needs to be modified compared with younger patients (Table 2). Dosing the drug at doses that are equivalent to those of younger patients can lead to higher drug levels, which can lead to alterations in hemodynamic status.34 In a study evaluating the pharmacokinetics of propofol in a multicenter platform, the induction doses of propofol in the elderly were as low as 1 mg/kg, far less than the conventional dose of 2 to 2.5 mg/kg in adults.35,36 Also, the metabolic clearance of propofol declines after age 60 years. This finding was corroborated in another study that noted that propofol infusions resulted in drug concentrations that were 20% to 30% higher in geriatric patients compared with younger patients.37 Besides the clearance effect, one study presented information on the sensitivity of geriatric patients to propofol compared with younger patients.37 The clinical effect of propofol was measured via electroencephalogram (EEG) in adults aged 25 to 81 years and elderly patients were noted to have a 30% increased sensitivity to propofol versus younger cohorts. The investigators concluded that reductions in propofol dose as determined by the study results are not solely related to sensitivity but are also related to the altered clearance of the drug, as noted previously.15

**Etomidate**

This potent induction agent is a sedative hypnotic agent with minimal hemodynamic effects when administered at induction doses. The minimal cardiovascular effects of etomidate make it a preferred agent in emergencies and for patients who cannot tolerate wide alterations in blood pressure during the induction phase of anesthesia. The drug is metabolized by ester linkage hydrolysis to inactive metabolites, which are then largely excreted in the urine. It is highly protein bound (75%), primarily to albumin.
A 50% decrease in dosage reduction is recommended in patients aged 80 years and older. The adjustment results from a reduced clearance of the drug with a decreased Vd.38

**Ketamine** The NMDA receptor antagonist ketamine is used as an induction agent and for sedation. As an antagonist to this complex, this agent shows antinociceptive effects. This agent also has a neuroprotective effect by decreasing the risk of ischemia-related apoptosis, which may lead to neuronal cell loss.39

Ketamine has also been advocated as an agent against POCD in elderly patients to decrease the risk of altered cognitive function after ophthalmic surgery. The recommended dose for this application is 0.3 mg/kg. This agent leads to less hypotension when given for sedation compared with propofol.7

**Benzodiazepines** The use of perioperative benzodiazepines increases the risk of postoperative delirium and should be used judiciously in geriatric patients.40 One study evaluated midazolam, a common preoperative sedative, and noted that, after age 65 years, dosing of midazolam should be decreased compared with younger patients.41 Midazolam clearance is reduced by 30% in 80-year-old patients compared with patients in their 20s. As a result, the dose of midazolam in geriatric patients should be decreased by at least 25%.42 In addition, the geriatric brain is much more sensitive to midazolam, as is the case with propofol.

**Dexmedetomidine** Dexmedetomidine is used in for both maintenance of anesthesia and for sedation in the intensive care unit. In the elderly, the context-sensitive half-time of dexmedetomidine is prolonged and could result in prolonged sedation.

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**Table 2**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Effect</th>
<th>Recommended Dosing Adjustments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sedative/hypnotics</td>
<td>Exaggerated hypotension with bolus dosing, smaller Vd and reduced clearance</td>
<td>Propofol: 20%–50% reduction in bolus dosing and infusion rates, Etomidate: 20%–50% reduced bolus dose</td>
</tr>
<tr>
<td>Opioids</td>
<td>• Increased sensitivity</td>
<td>Fentanyl/remifentanil: 50% reduction for bolus infusion rates, age &gt; 80 y, morphine, hydromorphone, meperidine: reduced doses because of concern over active metabolites</td>
</tr>
<tr>
<td>• Delayed renal clearance of opioid metabolites</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>• Increased sensitivity, delayed renal clearance of metabolites, increased risk for delirium/POCD</td>
<td>Midazolam: reduce dose by 25%–75%, not recommended for geriatric patients</td>
</tr>
<tr>
<td>Muscle relaxants</td>
<td>• Delayed clearance caused by declining renal and hepatic function</td>
<td>Succinylcholine: no change, rocuronium: dosing intervals less frequent, cis-atracurium: no change</td>
</tr>
<tr>
<td>Inhalational agents</td>
<td>Minimum alveolar concentration decreases 6% per decade after age 40 y</td>
<td>Reduced MAC as per iso-MAC, consider BIS to guide depth</td>
</tr>
</tbody>
</table>

*Abbreviations:* BIS, bispectral index; MAC, minimal alveolar concentration.
According to Iirola and colleagues, 80-year-old patients have a 25% decrease in clearance compared with 60-year-olds.

**Muscle relaxants/reversal agents**

**Succinylcholine** The depolarizing neuromuscular blocker succinylcholine is used to facilitate rapid conditions for intubating patients in the perioperative period. The agent is degraded into the components succinic acid and choline by the butyl cholinesterase enzymes. With aging, levels of this plasma cholinesterase enzyme decrease; however, this alteration does not typically lead to prolonged action of succinylcholine.

**Rocuronium** This nondepolarizing agent is primarily metabolized in the liver and excreted in the bile. Typically, rocuronium has a rapid onset of action with intermediate duration of action. Dosing of this agent is 0.45 to 1.0 mg/kg to facilitate intubating conditions and the drug has been used in maintenance states as an infusion. Although rocuronium is dosed based on ideal body weight in younger patients, elderly patients may require dose adjustment. One study evaluated the neuromuscular effects of rocuronium in elderly and younger patients, both with and without renal disease. The duration of neuromuscular blockade was prolonged in elderly patients compared with younger patients for both the control group and for those patients with renal disease. A slower onset time of the agent and a prolonged duration has been compared in other studies.

**Sugammadex** Sugammadex is a modified gamma-cyclodextran compound that is a selective vecuronium and rocuronium binding agent. It is biologically inactive and does not bind to plasma proteins, but to the neuromuscular blocking agents. Sugammadex is minimally metabolized, with three-fourths of the agent eliminated unchanged in the urine. Rocuronium combines with sugammadex in a binding site, which leads to a decrease in the free concentration of rocuronium in the plasma. In the geriatric population, sugammadex is effective in reversing neuromuscular blockade, albeit in a delayed fashion. In a phase 3a, multicenter, parallel-group, open-label study, it was noted that the time to recovery after administration of sugammadex to a train of 4 ratio of 0.9 was 3.6 minutes in geriatric patients versus 2.3 minutes in younger adults. Sugammadex clearance was approximately 50% lower in the elderly patients than in younger adults. Regardless, no dose adjustment is recommended in elderly patients with normal organ function; however, because renal function is reduced in the elderly, dosing may need to be individually adjusted.

**Cisatracurium** Cisatracurium is a nondepolarizing agent present as one of 10 stereoisomers of atracurium. It is 4 to 5 times more potent than atracurium, with similar duration of neuromuscular blockade, and with less histamine release. This agent is eliminated via spontaneous degradation through Hoffman elimination and ester hydrolysis by plasma esterases. Hoffman elimination is a pH-dependent and temperature-dependent processes. From 77% to 80% of the drug is eliminated via Hoffman elimination; 10% to 15% is excreted unchanged in the urine. In geriatric patients versus young patients, the duration of neuromuscular blockade was not altered, although the time to onset of neuromuscular blockade was delayed by 1 minute, likely because of changes in circulation time. Despite having a larger Vd compared with younger patients, the elderly patients had a minimal increase in elimination half-life. Cisatracurium clearance is unaffected by age.

**Anticholinesterase agents**

Anticholinesterase agents in the elderly have a theoretic risk of cardiac dysrhythmias and the presence of conduction delays. To counteract this muscarinic effect, the
antimuscarinic agents are administered (preferably glycopyrrolate because there is less central effect of this agent than of the tertiary amine atropine). Some studies have noted an effect on the duration of action of neostigmine\textsuperscript{55} versus other agents; compared with younger patients, the duration of action was prolonged in geriatric patients.\textsuperscript{56}

**Opioids** Providers need to be cautious about administering opioids because effects in elders are caused by an increase in sensitivity to the agent. Risk of opioid overdose is caused by an increase in central nervous system sensitivity to opioids with age.

**Fentanyl** The pharmacokinetics and pharmacodynamics of this agent have been evaluated in the aging population.\textsuperscript{57} Age was not found to have any effect on the pharmacokinetics of fentanyl. Sufentanil, alfentanil, remifentanil, and fentanyl are approximately twice as potent in elderly patients, primarily because of an increase in brain sensitivity to opioids rather than pharmacokinetic changes.\textsuperscript{29} Except for a modest change in rapid intercompartmental clearance, the Vd is not changed compared with younger adults. The elderly brain is twice as sensitive to fentanyl and alfentanil as younger brains, although with considerable variability. As a result, providers should consider dose adjustment in geriatric perioperative patients.

**Remifentanil** This short-acting selective mu-receptor antagonist is typically used as an infusion for rapid analgesia because it is metabolized by nonspecific esterases. This property makes it ideal for patients with liver and/or renal dysfunction. However, the pharmacokinetics and dosing of this potent opioid require special consideration. Minto and colleagues\textsuperscript{58,59} found that the volume of the central compartment decreased by 50% from age 20 to 80 years and the clearance decreased by 66%. As a result, age and lean body mass were determined to be important covariates affecting the pharmacokinetics of remifentanil. This finding has been corroborated elsewhere.\textsuperscript{60} Comparing 25-year-olds and 80-year-olds getting remifentanil infusions, the clearance values are expected to decrease by 30% and central compartment values to be reduced by at least 25%.

After having established the changes in the compartments in the elderly population, the clinical effects and changes were noted compared with younger adults.\textsuperscript{59} EEG depression as a function of sedation was noted across the age spectrum. The EC50 (effective concentration giving half-maximal response) for EEG depression decreased by approximately 50% from age 20 to 80 years. This result matched the effect of age on fentanyl potency.

Pharmacokinetic/pharmacodynamic modeling of this agent supports a 50% reduction of the bolus dose in geriatric patients versus a 20-year-old patients and a 30% to 50% reduction in infusion dosing. Elderly patients are at risk for delayed emergence without dosing adjustments.\textsuperscript{58}

**Morphine** Morphine dose adjustment needs to occur because of multiple factors. Morphine is processed by conjugation in the liver to morphine-3 glucuronide and morphine-6 glucuronide. Morphine-3 glucuronide is a neurotoxic agent that can lead to seizures. Morphine-6 glucuronide has analgesic properties. Both are renally cleared and have decreased clearance in the elderly.\textsuperscript{51}

**Inhaled agents** Perioperative physicians also need to consider unique factors in the geriatric population when adjusting inhaled anesthetic concentrations. The minimal alveolar concentration (MAC) to surgical stimulus decreases by 6% for every decade of life.\textsuperscript{62} Currently used agents are considered individually, with unique considerations for
each agent. In addition, the use of iso-MAC scales is used to allow for the addition of nitrous-oxide/oxygen to inhaled potent agents. End-expired agent in terms of MAC is graphed versus age of subject and data points presented for End-expired agent in 100% oxygen, 67% nitrous oxide and 50% nitrous oxide.63

**Sevoflurane** Sevoflurane is perhaps the most commonly used agent for maintenance of inhaled anesthesia. The MAC for sevoflurane was noted to be 1.48, decreased from children and adults, with a calculated ED95 (the effective dose required to prevent 95% of patients from moving) of 1.98%.64 This age-related change in dosage of sevoflurane is corroborated by the finding of midlatency auditory evoked potentials (MLAEPS) as a marker for anesthetic depth. Elderly patients need lower anesthetic concentrations of sevoflurane than younger patients to achieve a similar MLAEP level.65 It has been evaluated as an agent for inhaled inductions in ambulatory geriatric patients compared with propofol induction. The sevoflurane inhaled induction patients were noted to have less alteration in mean arterial pressure and systolic pressure versus their propofol cohorts. This finding would lead to fewer instances of hemodynamic alteration for the induction phase of anesthesia.66

Another study evaluated sevoflurane induction in patients undergoing esophageal resection to assess for any effects on POCD in patients receiving sevoflurane anesthesia. Patients were placed into sevoflurane inhaled anesthesia, sevoflurane with preoperative methylprednisolone before potent agent, and intravenous propofol control.4 Cognitive assessment was performed before surgery and on days 1, 3, and 7 postoperatively along with evaluation for inflammatory and neurocognitive markers. The results indicated that the incidence of POCD was higher in patients under inhalational sevoflurane than in the other groups. Methylprednisolone was a salubrious pretreatment neuroprotective agent. Although these results are singular, for more invasive operations that may be time laborious, a multimodal regimen is advocated for neuroprotection.

**Desflurane** This insoluble inhaled anesthetic allows rapid redistribution and wake up with maintenance of potent anesthesia. For the geriatric population, a decrease in MAC is determined for geriatric patients, down to 5.1% for 80-year-old patients versus 8.3% in adults. This is an important consideration given the risk of tachycardia that can occur with rapid increases in anesthetic concentration of desflurane.

**Isoflurane** This agent has been used less because of the increased use of sevoflurane and desflurane. In the elderly, isoflurane decreases systemic pressure, cardiac index, and heart rate.

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