Geriatric Pharmacology
An Update

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KEYWORDS

• Geriatric • Elderly • Aging • Pharmacology • Physiology • Anesthesiology • Pharmacokinetic • Pharmacodynamic

KEY POINTS

- An aging worldwide population demands that anesthesiologists consider geriatrics a unique subset of patients requiring customization of practice.
- The physiology of elderly patients causes pharmacokinetic and pharmacodynamic changes that must be taken into consideration when planning and providing anesthetic care.
- The dosing of most commonly used anesthetic and analgesic agents must be adjusted for the safe practice and care of elderly patients.
- Because many rigorous studies often exclude geriatric patients from research populations, the establishment of best practices for the elderly deserves ongoing special attention and investigation.

INTRODUCTION

The geriatric population (>65 years) is growing much faster than the population as a whole, with projections of more than 100 million people greater than 65 years old in the United States population by the year 2060.[1] The number of adults aged 65 or older

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is expected to exceed half of the US population by the year 2020,[2] and likewise these patients are expected to represent a greater fraction of surgical patients with each coming year. Older adults already represent a majority of the surgical patient population for such specialties as cardiac surgery and ophthalmology.[2] Simultaneously, the elderly population is at greatest risk of morbidity and mortality with any given complication after surgery.[3,4] This magnifies the importance of tailored care for these patients by all providers involved in the surgical process, including anesthesiologists. It is well known that older adults require less anesthetic than their younger counterparts, a phenomenon largely attributable to declining organ function and reserve, including alterations in medication response due to pharmacokinetic (PK) and pharmacodynamic (PD) changes. The mechanisms underlying these changes should be well understood by all anesthesiologists in order to provide the safest care for older adults undergoing surgery.

PKs describes the manner in which the body affects a drug, whereas PDs describes the manner in which the drug affects the body. The specific PK and PD changes associated with aging include changes related to reduced end-organ function, receptor sensitivity, homeostasis patterns, concurrent medication use, and complexity of concomitant disease states. Changes in organ system function, body composition, nutritional state, and a lifetime of metabolic insults, including changes to DNA processing, can occur with wide variation between older patients. Such variety serves to complicate the effort to understand how drug activity changes with age.[5,6] Furthermore, older adults often are excluded from clinical trials due to comorbidity, despite their increased use of medication relative to other populations.[6,7]

Inadequate understanding of pharmacologic changes in geriatric patients undergoing anesthesia unfortunately is common and can have disastrous consequences. Since the advent of modern anesthesiology, however, great strides have been made in understanding how drug absorption, distribution, activity, and elimination change with age. This article discusses the major PK and PD changes associated with aging; the PD changes that occur in the neurologic, respiratory, and cardiovascular systems with aging for the most common anesthetics in use today also are covered. The final section discusses the PK and PD changes associated with aging and gives practical recommendations regarding the clinical applications of these principles with commonly used anesthetic medications.

PHARMACOKINETIC CHANGES IN THE ELDERLY

Drug Absorption

There are substantial changes in the aging gastrointestinal (GI) tract that have an impact on uptake and absorption of orally administered medications. Transmucosal absorption of medications seems preserved, as demonstrated in a study of transmucosal fentanyl administration in young and old patients without apparent difference in the incidence of negative side effects.[8] More substantial research has been directed toward changes in the stomach and distal GI tract. Commonly observed decreases in gastric acid secretion with resultant elevated gastric pH in the elderly can reduce absorption of medications that rely on ionization within the stomach for proper absorption distally. Furthermore, use of proton-pump inhibitors and antacids can interfere with drug ionization.[6,9–11] The stomach's role in absorption can be altered further by changes in gastric motility and transit time; slower gastric emptying time, decreased peristalsis, and slower colonic transit overall can be attributed to a loss of neuronal activity in the GI tract.[6,12,13] Conversely, gastric emptying time may be increased in

elderly patients due to a history of partial gastrectomy or use of laxatives or cholinergic agents, such as physostigmine. Increased or decreased gastric emptying can have variable impacts on drug absorption depending on a given drug's site of absorption.[10,14] Additionally, decreases in gastric blood flow, whether from chronic vascular disease or another cause, may play a role in preventing effective drug ionization and uptake.[9–11]

More distally, decreased peristalsis and slower colonic transit time due to neuron loss or other concomitant disease can have a further impact on drug absorption. Prolonged exposure of the digestive tract to medications or failure to efficiently deliver compounds to the site of absorption may be of greatest consequence when considering medications with low solubility or permeability.[6,12,13] In conjunction with these changes to the proximal GI tract, the peak concentration of a medication as well as the time it takes to reach it may be widely variable in older patients with multiple comorbidities. The ultimate bioavailability of orally administered drugs is influenced by the amount of drug absorbed by the GI mucosa, the amount of drug that flows unchanged to the liver, and the amount of first-pass metabolism that occurs. Hepatic mass may decrease as much as 25% to 35% with age, and flow may decrease as much as 35% to 40%[15,16]; however, in the absence of concomitant disease, the structure of the liver and its synthetic function seem preserved with age and the extent to which liver mass and blood flow have an impact on first-pass metabolism remains unclear.[7] Understanding the liver's role in drug bioavailability is complicated further by the variability in cytochrome p pathways and the large number of drugs that interact with them. Further research into how each of these pathways is affected with age is required for a better understanding of medication-specific changes in the elderly.

Drug absorption through other administration methods also seems impacted by age. Older adults were found more vulnerable to the side effects of transdermal fentanyl than younger subjects.[17] Although the enhanced vulnerability of the elderly to narcotics likely is attributable to multiple physiologic changes, older adults experience thinning of the epidermis and structural weakening of the dermis that may alter and likely augment transdermal drug absorption.[18–20]

Older adults are also known to be more vulnerable to the effects of inhaled anesthetics, and the decreased minimum alveolar concentration (MAC) of inhaled anesthetics in the elderly has been widely accepted.[21] Lung physiology has been researched extensively and changes dramatically with age. Older patients demonstrate reduced airway elasticity, which can be enhanced by chronic smoking, as well as decreased chest wall compliance due to intervertebral disk height loss, ossification of costal cartilage, and weakening of respiratory muscles. These changes contribute to an overall profile of decreased tidal volume, loss of functional residual capacity, increased closing capacity, and ventilation/perfusion mismatch.[22,23] These changes reduce the efficiency of gas exchange across the alveolar membrane, likely translating to altered translocation of inhaled anesthetics impacting both induction and emergence. The uptake and offloading of inhaled anesthetics also are particularly vulnerable to acute changes in cardiac function. This has been observed in cases of significant and sudden drops in cardiac output correlated with dramatic increases in end-tidal volatile anesthetic, likely due to enhanced uptake of the anesthetic due to slower transit times through the pulmonary vasculature.[24] Although a full review of the cardiac changes with age is outside of the scope of this section, significant changes to cardiac output and flow through the pulmonary vasculature are common in elderly patients and affect uptake and offloading of volatile anesthetics.

Drug Distribution

Older adults experience clinically significant change in their volume of distribution due to a few key physiologic changes. Total body water decreases by 10% to 15% in elderly compared with younger persons.[25] This effectively decreases the volume of distribution for hydrophilic agents in elderly persons and, therefore, water-soluble drugs have higher peak plasma concentrations at a given dose compared with younger patients. Decreases in parenteral loading doses of 10% to 20% are recommended in older adults.[6,15] Although total body water decreases with age, there is an increased volume of distribution of lipophilic drugs due a combination of muscle wasting and increase in body fat, in particular central adiposity and visceral body fat with aging.[26,27] Body fat in older adults has been shown to increase up to 20% to 40%. Dosing for the parenteral loading of highly lipophilic drugs may be increased by approximately 10% to 20%.[6,15] Lipophilic drugs, however, have an increased elimination half-life and thus lead to drug accumulation.

Age-related changes in protein binding have been studied extensively. The pH of the drug and the protein binding should be taken into consideration when determining dosing adjustments in elderly patients. One notable change includes a linear decrease in serum albumin levels with increasing age. This decrease in serum albumin predominately affects highly protein-bound, acidic drugs because they more commonly bind albumin.[11] Even when there is a small reduction in the protein binding of extensively bound drugs, this may result in a clinically significant increase in free drug concentration.[11] There also is a slight increase in α_1-acid glycoprotein in elderly patients, however, which is probably due to age-associated inflammatory changes.[28] This increase in α_1-acid acid glycoprotein theoretically can affect the circulating free drug concentrations, particularly of lipophilic basic drugs[11] Notable anesthetic drugs that may be affected by age-related protein-binding changes are those highly extracted by the liver, extensively protein bound, and administered intravenously (IV).

In addition to a reduced central circulating volume in elderly patients, central organ perfusion undergoes change with aging. The aging brain is accompanied by a decrease in neuronal volume, which starts earlier in men but progresses more rapidly in women once it begins.[29] The aging brain also sustains a change in vascular distribution. Capillaries that normally are packed densely in areas of the brain that have higher processing demands decrease in number and show increased microvessel deformities starting in approximately the fifth decade of life.[30] Increasing age is associated with increasing blood-brain barrier permeability,[31] which can allow inappropriate passage of mediators from the plasma into the central nervous system (CNS).

Older adults have increased sensitivity to IV anesthetic agents due to fundamental changes in drug binding and distribution, described previously. Unfortunately, the changes in drug effect vary between patients of different ages in a nonlinear, exponential fashion.[32] Likewise, changes in drug effect with age depend heavily on PK and PD parameters for a given drug, with wide variation between different medications, even within a given class. Thus, easy-to-remember recommendations for medication dose adjustments applicable to multiple drugs over a range of patient ages, comorbidities, weights, nutritional statuses, and so forth, are impossible. Even so, most experts believe it prudent to significantly reduce medication doses in older patients.[33,34] Examples include fentanyl, haloperidol, lidocaine, midazolam, and propofol,[34] for which dose reductions should be considered.

Drug Metabolism and Excretion

Metabolism of drugs is another area of PK change in older adults. Hepatic metabolism of drugs is affected by aging due to a decrease in hepatic blood flow of approximately 40% in elderly patients,[6] thereby decreasing rate of drug delivery. Additionally, there is an age-related decrease in liver mass, reducing hepatic microsomal enzymes and extending the half-life of many drugs, including anesthetics. Because many older adults have multiple chronic comorbidities that require use of medicines, anesthetic drug metabolism is effectively further decreased due to saturation of the reduced number of hepatic microsomal enzymes. When controlling for volume of distribution, terminal elimination half-life of fentanyl was markedly prolonged in the elderly (patients more than 60 years old) compared with patients less than 50 years old (945 min vs 265 min).[33] The exact influence a reduction of hepatic microsomal enzymes has on anesthetic dosing, however, in the aging population is less clear, because other studies evaluating the effect of age on anesthetic drug clearance have been inconclusive.[35,36]

It is currently unknown whether extrahepatic metabolism of drugs is impacted by aging. Pulmonary metabolism of drugs is well described but the implications of lung metabolism in older adults, particularly for anesthetic drugs, have not been well studied. The extent to which ester metabolism changes in the elderly also is unclear, with conflicting studies regarding different commonly used agents. Ornstein and colleagues[37] studied changes in ester metabolism in older (65–82 years old) compared with younger (30–49 years old) individuals and found that although the onset of action of cisatracurium was delayed, the elimination half-life was unchanged, suggesting there is no difference in ester metabolism in the elderly. APK model of remifentanil, however, showed a decrease in metabolism with age.[38]

Renal function decreases in older adults, with a progressive reduction in renal mass, creatinine clearance, and glomerular filtration rate. Some studies have shown the decrease in glomerular filtration rate to be approximately 1 mL/min/1.73 m^2 per year after approximately 40 years of age, which is due to a reduced number of functioning glomeruli.[39] Serum creatinine is commonly used as a marker of renal function and, therefore, drug elimination, but it should be recognized that this is affected by muscle mass, physical activity, protein intake, and active secretion of creatinine by the renal proximal tubules.[39] Because of this reduction in renal clearance, the plasma half-life of a renally excreted drug is prolonged and the steady-state concentration increases.[11] There is a reduction in renal blood flow with age after the fourth decade of life, resulting in a 10% decrease with each decade of life.[40] Accompanying this decrease in renal blood flow is a decrease in autoregulation of volume status and autoregulation of blood flow in hypertensive and hypotensive states, called renal vascular dysautonomy.[41,42] Drugs that are renally cleared by the kidney and eliminated unchanged also warrant a reduction in dosing in the elderly.

There seems to be heterogeneity in geriatric PKs, which likely is due to a difference in fit versus frail older adults. Physiologic changes that affect PKs in older adults are certainly affected by the increased prevalence of chronic comorbidities. More research is needed, however, to further categorize pharmacokinetics in relation to chronologic versus functional aging.[43]

PHARMACODYNAMIC CHANGES IN THE ELDERLY

Central Nervous System

It is well known that older adults are more sensitive to inhaled anesthetics and opioids than younger adults. MAC correlates with the degree to which an anesthetic enhances

the function of γ-aminobutyric acid (GABA)-A receptors in the brain, and PET scans have shown this interaction dependent on the blood concentration of the anesthetic.[22,44,45] The MAC value for volatile anesthetics decreases by 6% per decade and that for nitrous oxide decreases by approximately 8% per decade over the age of 40 years.[46] Similarly, the best research suggests that older adults are more sensitive to sedative and possibly deliriogenic effects of opioids, and thus dosing should be reduced.[47] At least 1 prospective trial currently is ongoing that may give more insight into whether opioid-free anesthesia is of benefit.[48]

Overall, the CNS of older adults is approximately 30% more sensitive to propofol than younger patients, which has been reported for both induction doses and infusions (**Fig. 1**).[49] During induction, patients greater than 70 years old reach significantly deeper electroencephalographic (EEG) stages and need more time until a normal EEG returns compared with younger patients.[50] Propofol has favorable effects on CNS parameters, because it lowers cerebral metabolic rate ($CMRO_2$), cerebral blood flow (CBF), and intracranial pressure (ICP).[51] When given as a bolus, propofol can lower the mean arterial pressure (MAP) considerably, possibly lowering cerebral perfusion pressure (CPP) below a critical level. This latter consideration is of prime importance in older adults because they are more apt to have critical carotid or aortic valvular stenosis. The range of cerebral autoregulation may be altered significantly if the patient has chronic hypertension; these patients are more apt to have blood pressure lability with induction. Thus, it seems that increasing age causes changes in the brain that increase the effective potency of propofol for the geriatric patient.

The mechanism of action of benzodiazepines on the GABA receptor (and its various subtypes) is reasonably well understood.[52–54] The onset and duration of action of a bolus IV administration of midazolam depend largely on the dose given and time at which the dose is administered; the higher the dose given over a shorter time (bolus), the faster the onset. The time to establish equilibrium between plasma concentration and EEG effect of midazolam is approximately 2 minutes to 3 minutes and is not affected by age.[55] Although there may not be a PK change, however, there seems to be a clear PD effect of increased risk of delirium with benzodiazepines, especially in older adults, when used as an infusion in the intensive care unit (ICU).[56,57] Whether

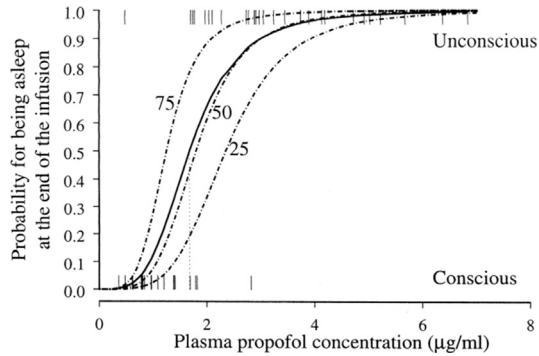

Fig. 1. Effect of age on propofol pharmacodynamics. This logistic regression shows the age-related probability of being asleep after a 1-hour infusion of propofol. A 75-year-old patient is 30% to 50% more sensitive to propofol than is a 25-year-old patient. (*From* Schnider TW, Minto CF, Shafer SL, et al. The influence of age on propofol pharmacodynamics. Anesthesiology 1999;90(6):1510; with permission.)

this is true for small doses in the perioperative period has not been definitively shown.[58] Recommendations by the American Geriatrics Society (with representation from both surgery and anesthesiology) recommend avoidance of benzodiazepines, limiting their use to special circumstances.[59]

Etomidate induces changes in CBF, $CMRO_2$, and ICP similar to propofol, but it does not result in the same changes in MAP.[60] This is of particular importance in the older patient at risk for ischemic stroke secondary to carotid occlusion. Overall, there are no PD changes with age with respect to etomidate as measured by EEG,[60] but etomidate is associated with a higher rate of postoperative nausea and vomiting than other induction drugs, and this seems unchanged in the elderly.[61,62]

Ketamine has received particular attention in older adults over the past few years because there was a concern that its use may be associated with increased delirium after surgery. Several studies in the past decade have shown a decreased incidence of postoperative delirium after cardiopulmonary bypass in anesthetized elderly patients treated with ketamine (0.5 mg/kg–1 mg/kg) compared with placebo.[63,64] More recently, a large international, multicenter, randomized controlled trial demonstrated that ketamine neither increased nor decreased postoperative delirium.[65] A planned substudy showed that intraoperative ketamine infusions were not associated with any reduction in new depressive symptoms after surgery, which is interesting given the interest of prolonged outpatient ketamine infusions for reducing depression.[66] Overall, there are no reports of PD changes in the elderly compared with in young adults.

Finally, dexmedetomidine has emerged as a medication frequently used for sedation in the perioperative period and the ICU setting, as discussed previously. Few studies have addressed whether there are PD changes with aging that would affect dexmedetomidine dosing. One small study comparing elderly and young patients showed no difference in PD parameters, although the elderly did require more interventions from a hemodynamic perspective.[67]

Respiratory System

In addition to age-related PD changes in the CNS, there are important age-related changes in the respiratory system that should be understood in order to provide optimal care related to anesthesia pharmacology. Propofol causes dose-related depression of ventilation.[68,69] In standard induction doses, propofol causes apnea whereas infusions for sedation cause increasing levels of respiratory depression.[70] Additionally, airway reflexes are depressed and both the hypoxic and hypercapnic ventilatory responses are blunted with propofol administration, all of which are greatly enhanced by the addition of opioids.[70–74] Due to changes in pulmonary anatomy and mechanics in older adults (increased closing capacity, decreased functional residual capacity, and decreased strength of cough to clear secretions), all these effects of propofol can have profound consequences.[75] Similar to propofol, older age and debilitating disease increase the incidence and severity of respiratory depression with midazolam.[76] Conversely, etomidate, dexmedetomidine, and ketamine all cause less respiratory depression in older patients than benzodiazepines or propofol, even in induction doses.[77–80] This advantage can make these medications useful choices in the setting of an elderly patient with diminished respiratory reserve, although care would need to be taken related to cardiovascular effects of dexmedetomidine.

Cardiovascular System

Another major consideration in older adults involves the interaction of PD changes in the cardiovascular system related to anesthetic agents. Propofol can cause profound

changes in MAP through reduced vascular resistance when given in induction bolus doses.[81] In the young adult patient, this is well tolerated and easily reversed by airway manipulation. In elderly patients, many of whom are hypertensive at baseline, the degree of hypotension is increased due to reduced baroreceptor reflex responses, a higher likelihood of ventricular dysfunction, and greater likelihood of hypovolemia due to chronic diuretic therapy.[82] As such, propofol may be avoided for patients with severe cardiovascular disease (eg, severe/critical aortic stenosis or ventricular dysfunction). Many of these deleterious effects can be greatly reduced if a slower induction is performed rather than a rapid bolus.[83]

Unlike propofol, etomidate has minimal effects on the cardiovascular system during induction. Reduction in vascular resistance is minimal, and myocardial contractility, heart rate, and cardiac output usually are unchanged.[84] These aspects of the PD profile of etomidate make it useful for older adults who may have reduced preload, coronary artery disease, valvular disease, or reduced ventricular function. Like etomidate, midazolam alone has modest hemodynamic effects. But, the addition of opioids, especially fentanyl and sufentanil, to benzodiazepines result in greater reductions in blood pressure than either alone.[85–87] Ketamine also has a favorable hemodynamic profile, even in the elderly. It can cause transient increases in heart rate, blood pressure, and cardiac output but these parameters return to baseline within minutes and can be controlled with a short-acting β-blocker, such as esmolol.[88] Overall, titrated doses are well tolerated in older adults, including the critically ill, but ketamine should be used with great caution in patients with severe stenotic valvular lesions, active myocardial ischemia, or decompensated heart failure.

Finally, dexmedetomidine has been shown to be of benefit in reducing delirium in the ICU setting (likely by avoiding benzodiazepines). It can, however, have significant hemodynamic effects through bradycardia and peripheral vasodilation. Accordingly, for the reasons discussed previously, the hemodynamic effects of dexmedetomidine tend to be more pronounced in elderly patients and this means dosing should be reduced or boluses administered more slowly than in young adults.[89]

IMPLICATIONS FOR PRACTICE: ANESTHETIC DOSING RECOMMENDATIONS IN THE ELDERLY

Opioids

A large variety of opioids with heterogeneous pharmacokinetics are available for perioperative use, with properties ranging from lipophilic to hydrophilic and clearance by the liver or in plasma, with and without active or toxic metabolites. Coverage of the breadth of opioids is beyond the scope of this article, but in general, older adults experience prolonged clearance of morphine, fentanyl, remifentanil, and meperidine but not sufentanil.[33,90–92] Reduced renal clearance of active or toxic metabolites make meperidine and morphine particularly risky in older or renally impaired individuals. In contrast, the PD changes with aging are more uniform across medications. Older individuals are markedly more sensitive to the analgesic effects as well as the sedative and respiratory depressant side effects of opioids.[93,94] Considering the PD and PK changes and their interindividual variability, opioid titration in the elderly should proceed carefully, with significantly reduced doses (25%–50%), longer redosing intervals, and avoidance of drugs with toxic metabolites.

Benzodiazepines

Although PK changes in midazolam do not affect drug onset, clearance of the drug is reduced by up to 30% with increased age, resulting in prolonged drug effect.[95] PD

changes result in increased sensitivity to benzodiazepine effect with age or comorbid conditions. Early work advised a dose reduction of 20% to 50% in older patients and those with ASA physical status of 3 or 4.[96] Dose reduction of 75% in 90-year-old patients compared with 20-year-old patients produces similar sedative effects (Fig. 2).[97] The deliriogenic effects of benzodiazepine infusions in elderly and critically ill patients are well documented and warrant some hesitation when administering even low-dose midazolam in the elderly. This is especially true when opioid coadministration is planned, due to synergistic respiratory depression.[98,99] In summation, benzodiazepines should be used cautiously at significantly decreased doses in the elderly (if they are used at all) (Table 1).

Propofol

The overall effects of propofol are pronounced in elderly patients, resulting in higher plasma drug levels, increased sensitivity, and reduced clearance.[49,82,83,100] Suggested alterations in propofol administration with age include a 20% reduction in induction dose, a decrease in speed of induction dose administration, and a 30% to 50% reduction in infusion rates for anesthetic maintenance.[97] For example, a 75 year old requires only half the maintenance infusion rate that a 25 year old would receive (Fig. 3). The context-sensitive half-time of propofol is approximately 20 minutes to 30 minutes after a 1-hour to 2-hour infusion in the elderly compared with only 10 minutes to 15 minutes in younger patients. The practical effect of this is that propofol infusions should be stopped significantly earlier in the elderly to allow for timely awakening and recovery[101] (see Table 1).

Etomidate

Etomidate PD parameters have not been shown to vary based on age, although PK factors do change. Aging decreases etomidate clearance, lengthens elimination

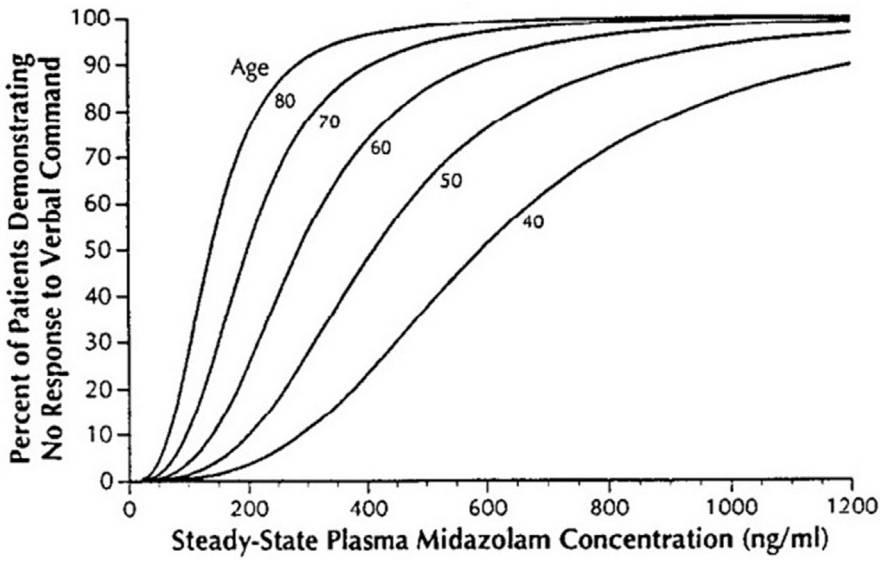

Fig. 2. Response curves to verbal commands in patients of various ages at varying plasma levels of midazolam. This demonstrates a pharmacodynamic change associated with aging in response to midazolam. (*From* Jacobs JR, Reves JG, Marty J, et al. Aging increases pharmacodynamic sensitivity to the hypnotic effects of midazolam. Anesth Analg 1995;80(1):143–148; with permission.)

Table 1
Uses and doses of commonly used nonopiate drugs

Drug	Sedation Dose (Intravenous)	Induction/Bolus Dose	Maintenance/ Infusion Dose	Dose Reduction (%) for Older Adults
Dexmedetomidine	0.5–1 μg/kg[a]	0.5–3 μg/kg[a]	0.1–2.5 μg/kg/h	30–50
Etomidate	N/A	0.2–0.4 mg/kg	N/A	20–50
Ketamine	0.2–0.5 mg/kg	1–2 mg/kg	10–20 μg/kg/min	0/unknown
Midazolam	0.02 mg/kg	0.025–0.1 mg/kg	0.3–1.5 μg/kg/min	20
Propofol	25–50 μg/kg/min	1.0–1.5 mg/kg	75–150 μg/kg/min	20
Thiopental	N/A	2–5 mg/kg	N/A	20

[a] Over 10 minutes to 20 minutes.
Data from Refs.[109,112,118–121]

half-life, and, most significantly, decreases the initial volume of distribution, raising drug plasma levels relative to younger controls. These PK changes are significant, with a 50% to 66% reduction required for anesthetic induction in 80 year olds compared with 20 year olds.[102] (see **Table 1**). Although it is prized for its hemodynamic stability during induction of anesthesia compared with other IV anesthetic agents, etomidate does produce significant, clinically relevant suppression of the adrenocortical system lasting 6 hours to 8 hours with single doses.[62] In patients experiencing sepsis or trauma, etomidate can suppress cortisol levels for 24 hours to 72 hours. This potent suppression of cortisol synthesis occurs even at low doses. A recent meta-analysis did not find any effects, however, on mortality in critically ill patients.[103] Additionally, repeated use of etomidate for electroconvulsive therapy in patients who are not critically ill does not seem to have any harmful effects and likely promotes better seizure duration.[104]

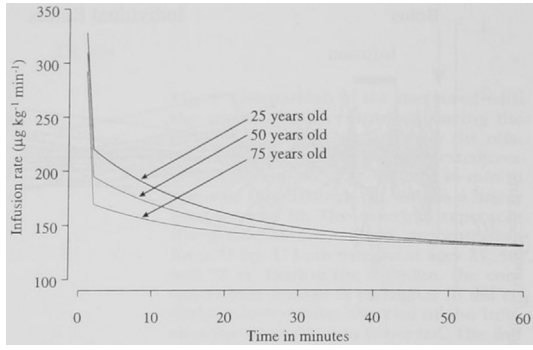

Fig. 3. Effect of age on propofol pharmacodynamics with a computer-controlled target-controlled infusion. In younger people, higher infusion rates must be maintained during the first 20 minutes to 30 minutes. In elderly people, after the first minute, a constant infusion rate is adequate for maintaining a constant plasma concentration. A 75-year-old patient is 30% to 50% more sensitive to propofol than is a 25-year-old patient. (*From* Schnider TW, Minto CF, Gambus PL, et al. The influence of method of administration and covariates on the pharmacokinetics of propofol in adult volunteers. Anesthesiology 1998;88(5):1180; with permission.)

Ketamine

Studies evaluating ketamine anesthesia do not provide guidance on dosing adjustments with age.[88,105] Studies of age-related dose adjustments for its modern usage as an analgesic given in subanesthetic doses are lacking. The impact of subanesthetic doses of ketamine on outcome varies by study, but there is no strong evidence of benefit or harm on postoperative cognitive outcomes or rates of delirium.[63,65,106,107] Because recommended doses for subanesthetic ketamine vary by an order of magnitude depending on the source, providing a dose recommendation is outside the scope of this discussion[108] (see **Table 1**).

Dexmedetomidine

Although the PKs of dexmedetomidine were not previously believed to vary with age, more recent work suggests a prolonged clearance and increased context-sensitive half-time in older adults.[109] In patients with hypoalbuminemia, these changes are more pronounced. Changes in dexmedetomidine PDs have not been elucidated, so the increased effects of the drug in the elderly may reflect either the PK changes or a combination of PD and PK changes. Regardless, a dose reduction of 33% is recommended for dexmedetomidine in the elderly, with titration to the appropriate level of sedation.[110] Adjustments should be made to the doses used in younger individuals for both bolus (0.5–1.0 μg/kg over 10 minutes) and infusion (0.2–1.0 μg/kg/h) dosing.[109] Although dexmedetomidine side effects, such as hypotension and bradycardia, are more common in the elderly (especially with bolus dosing), the drug offers several advantages, such as decreases in anesthetic requirements, opioid doses, agitation scores, and delirium incidence.[110–112] (see **Table 1**).

Nondepolarizing Neuromuscular Blockers

The PD parameters for neuromuscular blocking (NMB) drugs from the tetrahydroisoquinoline class (cisatracurium) and aminosteroid class (rocuronium and vecuronium) do not change with age. This means that age-related differences in clinical effect are entirely explained by PK changes, with no difference in receptor sensitivity related to aging.[113] Clearance of rocuronium, primarily by the liver, decreases with age, resulting in longer elimination half-life and prolonged drug effect in older adults. To demonstrate the magnitude of this difference, 1 study showed the half-life of a single 0.6 mg/kg-dose rocuronium in septuagenarians to be 98 minutes, which is 16 minutes longer than in younger controls.[113] Thus, the redosing interval for rocuronium should be longer in the elderly.

Cisatracurium is degraded largely by Hofmann elimination, with clearance independent of age and an only slightly increased volume of distribution and elimination half-life in the elderly. Onset in older patients is 1 minute slower (3.4 minutes vs 2.5 minutes), possibly related to slower circulation time.[113] For cisatracurium, duration of effect and redosing interval are only trivially lengthened whereas time to optimal intubating conditions may be delayed.

Sugammadex

Sugammadex, a selective relaxant binding agent, was approved in the United States in 2015 for reversal of NMB caused by rocuronium or vecuronium. Its γ-cyclodextrin structure selectively encapsulates aminosteroid NMB and is cleared primarily by the kidneys. Hypersensitivity (anaphylactic) reactions are the most severe complication related to sugammadex use, with a reported incidence of 0.039% in 1 study.[114] This is comparable in frequency to anaphylaxis with succinylcholine or rocuronium.

Other issues with sugammadex include an up to 5% risk of residual NMB when train-of-four (TOF) monitoring is not used to monitor relaxation and guide therapy.

Older adults differ in response to sugammadex therapy in several ways. They experience a slower spontaneous recovery of TOF, a slower onset of sugammadex effect, and a higher incidence of recurarization (worsening of TOF ratio) after sugammadex therapy compared with younger patients.[115] Patients with severe renal impairment also experience prolonged time to spontaneous recovery of TOF and slower onset of sugammadex.[116] This may be related to renal clearance of sugammadex and the sugammadex/NMB complex. In all groups, it is important to recognize that recovery to a TOF ratio greater than 0.9 is still significantly faster than with neostigmine reversal of NMB activity. All patients, but especially older adults and those with renal insufficiency, should receive TOF monitoring to appropriately guide sugammadex therapy.[117]

Volatile Anesthetics

As discussed previously, MAC requirements for all volatile anesthetics decrease with age.[21] Targeting a lower end-tidal anesthetic concentration in the elderly is advisable and iso-MAC charts or electronic resources can provide guidance.

SUMMARY

Providing the highest level of anesthetic care for elderly patients requires a thoughtful approach that accounts for the many physiologic PK and PD changes that occur with aging. Because older adults often are excluded from large trials due to age or comorbidity, developing a thorough understanding of their needs can be challenging but not impossible. Ongoing research, particularly with respect to the pharmacologic changes of aging, continues to expand understanding and improve care of older patients throughout the perioperative period.

REFERENCES

1. Bureau, U.S.C. From Pyramid to PIllar: a Century of change, population of the U.S. 2018. Available at: https://www.census.gov/library/visualizations/2018/comm/century-of-change.html. Accessed October 9, 2018.
2. Etzioni DA, Liu JH, Maggard MA, et al. The aging population and its impact on the surgery workforce. Ann Surg 2003;238(2):170–7.
3. Sankar A, Beattie WS, Wijeysundera DN. How can we identify the high-risk patient? Curr Opin Crit Care 2015;21(4):328–35.
4. Hamidi M, Joseph B. Changing epidemiology of the American population. Clin Geriatr Med 2019;35(1):1–12.
5. Crooks J. Aging and drug disposition–pharmacodynamics. J Chronic Dis 1983;36(1):85–90.
6. McLean AJ, Le Couteur DG. Aging biology and geriatric clinical pharmacology. Pharmacol Rev 2004;56(2):163–84.
7. Klotz U. Pharmacokinetics and drug metabolism in the elderly. Drug Metab Rev 2009;41(2):67–76.
8. Kharasch ED, Hoffer C, Whittington D. Influence of age on the pharmacokinetics and pharmacodynamics of oral transmucosal fentanyl citrate. Anesthesiology 2004;101(3):738–43.
9. Bender AD. Effect of age on intestinal absorption: implications for drug absorption in the elderly. J Am Geriatr Soc 1968;16(12):1331–9.

10. Evans MA, Triggs EJ, Cheung M, et al. Gastric emptying rate in the elderly: implications for drug therapy. J Am Geriatr Soc 1981;29(5):201–5.
11. Tumer N, Scarpace PJ, Lowenthal DT. Geriatric pharmacology: basic and clinical considerations. Annu Rev Pharmacol Toxicol 1992;32:271–302.
12. Orr WC, Chen CL. Aging and neural control of the GI tract: IV. Clinical and physiological aspects of gastrointestinal motility and aging. Am J Physiol Gastrointest Liver Physiol 2002;283(6):G1226–31.
13. Wiley JW. Aging and neural control of the GI tract: III. Senescent enteric nervous system: lessons from extraintestinal sites and nonmammalian species. Am J Physiol Gastrointest Liver Physiol 2002;283(5):G1020–6.
14. Nimmo WS. Drugs, diseases and altered gastric emptying. Clin Pharmacokinet 1976;1(3):189–203.
15. Le Couteur DG, McLean AJ. The aging liver. Drug clearance and an oxygen diffusion barrier hypothesis. Clin Pharmacokinet 1998;34(5):359–73.
16. Zeeh J, Platt D. The aging liver: structural and functional changes and their consequences for drug treatment in old age. Gerontology 2002;48(3):121–7.
17. Holdsworth MT, Forman WB, Killilea TA, et al. Transdermal fentanyl disposition in elderly subjects. Gerontology 1994;40(1):32–7.
18. Daly CH, Odland GF. Age-related changes in the mechanical properties of human skin. J Invest Dermatol 1979;73(1):84–7.
19. Montagna W, Carlisle K. Structural changes in aging human skin. J Invest Dermatol 1979;73(1):47–53.
20. Roskos KV, Maibach HI. Percutaneous absorption and age. Implications for therapy. Drugs Aging 1992;2(5):432–49.
21. Nickalls RW, Mapleson WW. Age-related iso-MAC charts for isoflurane, sevoflurane and desflurane in man. Br J Anaesth 2003;91(2):170–4.
22. Campagna JA, Miller KW, Forman SA. Mechanisms of actions of inhaled anesthetics. N Engl J Med 2003;348(21):2110–24.
23. Corcoran TB, Hillyard S. Cardiopulmonary aspects of anaesthesia for the elderly. Best Pract Res Clin Anaesthesiol 2011;25(3):329–54.
24. Kennedy RR, Baker AB. The effect of cardiac output changes on end-tidal volatile anaesthetic concentrations. Anaesth Intensive Care 2001;29(5):535–8.
25. Beaufrere B, Morio B. Fat and protein redistribution with aging: metabolic considerations. Eur J Clin Nutr 2000;54(Suppl 3):S48–53.
26. Lei SF, Liu MY, Chen XD, et al. Relationship of total body fatness and five anthropometric indices in Chinese aged 20-40 years: different effects of age and gender. Eur J Clin Nutr 2006;60(4):511–8.
27. Chang SH, Beason TS, Hunleth JM, et al. A systematic review of body fat distribution and mortality in older people. Maturitas 2012;72(3):175–91.
28. Grandison MK, Boudinot FD. Age-related changes in protein binding of drugs: implications for therapy. Clin Pharmacokinet 2000;38(3):271–90.
29. Small SA. Age-related memory decline: current concepts and future directions. Arch Neurol 2001;58(3):360–4.
30. Trollor JN, Valenzuela MJ. Brain ageing in the new millennium. Aust N Z J Psychiatry 2001;35(6):788–805.
31. Farrall AJ, Wardlaw JM. Blood-brain barrier: ageing and microvascular disease–systematic review and meta-analysis. Neurobiol Aging 2009;30(3):337–52.
32. Homer TD, Stanski DR. The effect of increasing age on thiopental disposition and anesthetic requirement. Anesthesiology 1985;62(6):714–24.
33. Bentley JB, Borel JD, Nenad RE Jr, et al. Age and fentanyl pharmacokinetics. Anesth Analg 1982;61(12):968–71.

34. Benet LZ, Hoener BA. Changes in plasma protein binding have little clinical relevance. Clin Pharmacol Ther 2002;71(3):115–21.
35. Lemmens HJ, Bovill JG, Hennis PJ, et al. Age has no effect on the pharmacodynamics of alfentanil. Anesth Analg 1988;67(10):956–60.
36. Lemmens HJ, Burm AG, Hennis PJ, et al. Influence of age on the pharmacokinetics of alfentanil. Gender dependence. Clin Pharmacokinet 1990;19(5):416–22.
37. Ornstein E, Lien CA, Matteo RS, et al. Pharmacodynamics and pharmacokinetics of cisatracurium in geriatric surgical patients. Anesthesiology 1996;84(3):520–5.
38. Minto CF, Howe C, Wishart S, et al. Pharmacokinetics and pharmacodynamics of nandrolone esters in oil vehicle: effects of ester, injection site and injection volume. J Pharmacol Exp Ther 1997;281(1):93–102.
39. McLachlan AJ, Pont LG. Drug metabolism in older people–a key consideration in achieving optimal outcomes with medicines. J Gerontol A Biol Sci Med Sci 2012;67(2):175–80.
40. Silva FG. The aging kidney: a review–part II. Int Urol Nephrol 2005;37(2):419–32.
41. Perico N, Remuzzi G, Benigni A. Aging and the kidney. Curr Opin Nephrol Hypertens 2011;20(3):312–7.
42. Karsch-Volk M, Schmid E, Wagenpfeil S, et al. Kidney function and clinical recommendations of drug dose adjustment in geriatric patients. BMC Geriatr 2013;13:92.
43. Kinirons MT, O'Mahony MS. Drug metabolism and ageing. Br J Clin Pharmacol 2004;57(5):540–4.
44. Zimmerman SA, Jones MV, Harrison NL. Potentiation of gamma-aminobutyric acidA receptor Cl- current correlates with in vivo anesthetic potency. J Pharmacol Exp Ther 1994;270(3):987–91.
45. Gyulai FE, Mintun MA, Firestone LL. Dose-dependent enhancement of in vivo GABA(A)-benzodiazepine receptor binding by isoflurane. Anesthesiology 2001;95(3):585–93.
46. Stevens WC, Dolan WM, Gibbons RT, et al. Minimum alveolar concentrations (MAC) of isoflurande with and without nitrous oxide in patients of various ages. Anesthesiology 1975;42(2):197–200.
47. Prostran M, Vujović KS, Vučković S, et al. Pharmacotherapy of pain in the older population: the place of opioids. Front Aging Neurosci 2016;8:144.
48. Beloeil H, Laviolle B, Menard C, et al. POFA trial study protocol: a multicentre, double-blind, randomised, controlled clinical trial comparing opioid-free versus opioid anaesthesia on postoperative opioid-related adverse events after major or intermediate non-cardiac surgery. BMJ Open 2018;8(6):e020873.
49. Schnider TW, Minto CF, Shafer SL, et al. The influence of age on propofol pharmacodynamics. Anesthesiology 1999;90(6):1502–16.
50. Schultz A, Grouven U, Zander I, et al. Age-related effects in the EEG during propofol anaesthesia. Acta Anaesthesiol Scand 2004;48(1):27–34.
51. Ludbrook GL, Visco E, Lam AM. Propofol: relation between brain concentrations, electroencephalogram, middle cerebral artery blood flow velocity, and cerebral oxygen extraction during induction of anesthesia. Anesthesiology 2002;97(6):1363–70.
52. Amrein R, Hetzel W, Bonetti EP, et al. Clinical pharmacology of dormicum (midazolam) and anexate (flumazenil). Resuscitation 1988;16(Suppl):S5–27.

53. Mohler H, Richards JG. The benzodiazepine receptor: a pharmacological control element of brain function. Eur J Anaesthesiol Suppl 1988;2:15–24.
54. Mould DR, DeFeo TM, Reele S, et al. Simultaneous modeling of the pharmacokinetics and pharmacodynamics of midazolam and diazepam. Clin Pharmacol Ther 1995;58(1):35–43.
55. Haefely W. The preclinical pharmacology of flumazenil. Eur J Anaesthesiol Suppl 1988;2:25–36.
56. Pandharipande PP, Pun BT, Herr DL, et al. Effect of sedation with dexmedetomidine vs lorazepam on acute brain dysfunction in mechanically ventilated patients: the MENDS randomized controlled trial. JAMA 2007;298(22):2644–53.
57. Barr J, Fraser GL, Puntillo K, et al. Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. Crit Care Med 2013;41(1):263–306.
58. Christe C, Janssens JP, Armenian B, et al. Midazolam sedation for upper gastrointestinal endoscopy in older persons: a randomized, double-blind, placebo-controlled study. J Am Geriatr Soc 2000;48(11):1398–403.
59. Mohanty S, Rosenthal RA, Russell MM, et al. Optimal perioperative management of the geriatric patient: a best practices guideline from the American College of Surgeons NSQIP and the American Geriatrics Society. J Am Coll Surg 2016;222(5):930–47.
60. Doenicke AW, Roizen MF, Kugler J, et al. Reducing myoclonus after etomidate. Anesthesiology 1999;90(1):113–9.
61. Watcha MF, White PF. Postoperative nausea and vomiting. Its etiology, treatment, and prevention. Anesthesiology 1992;77(1):162–84.
62. Forman SA. Clinical and molecular pharmacology of etomidate. Anesthesiology 2011;114(3):695–707.
63. Hudetz JA, Patterson KM, Iqbal Z, et al. Ketamine attenuates delirium after cardiac surgery with cardiopulmonary bypass. J Cardiothorac Vasc Anesth 2009;23(5):651–7.
64. Hudetz JA, Pagel PS. Neuroprotection by ketamine: a review of the experimental and clinical evidence. J Cardiothorac Vasc Anesth 2010;24(1):131–42.
65. Avidan MS, Maybrier HR, Abdallah AB, et al. Intraoperative ketamine for prevention of postoperative delirium or pain after major surgery in older adults: an international, multicentre, double-blind, randomised clinical trial. Lancet 2017;390(10091):267–75.
66. Mashour GA, Ben Abdallah A, Pryor KO, et al. Intraoperative ketamine for prevention of depressive symptoms after major surgery in older adults: an international, multicentre, double-blind, randomised clinical trial. Br J Anaesth 2018;121(5):1075–83.
67. Kuang Y, Zhang RR, Pei Q, et al. Pharmacokinetic and pharmacodynamic study of dexmedetomidine in elderly patients during spinal anesthesia. Int J Clin Pharmacol Ther 2015;53(12):1005–14.
68. Conti G, Dell'Utri D, Vilardi V, et al. Propofol induces bronchodilation in mechanically ventilated chronic obstructive pulmonary disease (COPD) patients. Acta Anaesthesiol Scand 1993;37(1):105–9.
69. Brown RH, Greenberg RS, Wagner EM. Efficacy of propofol to prevent bronchoconstriction: effects of preservative. Anesthesiology 2001;94(5):851–5 [discussion: 6A].
70. Blouin RT, Conard PF, Gross JB. Time course of ventilatory depression following induction doses of propofol and thiopental. Anesthesiology 1991;75(6):940–4.

71. Van Keer L, Van Aken H, Vandermeersch E, et al. Propofol does not inhibit hypoxic pulmonary vasoconstriction in humans. J Clin Anesth 1989;1(4):284–8.
72. Blouin RT, Seifert HA, Babenco HD, et al. Propofol depresses the hypoxic ventilatory response during conscious sedation and isohypercapnia. Anesthesiology 1993;79(6):1177–82.
73. Abe K, Shimizu T, Takashina M, et al. The effects of propofol, isoflurane, and sevoflurane on oxygenation and shunt fraction during one-lung ventilation. Anesth Analg 1998;87(5):1164–9.
74. Tagaito Y, Isono S, Nishino T. Upper airway reflexes during a combination of propofol and fentanyl anesthesia. Anesthesiology 1998;88(6):1459–66.
75. Zaugg M, Lucchinetti E. Respiratory function in the elderly. Anesthesiol Clin North America 2000;18(1):47–58, vi.
76. Parlak M, Parlak I, Erdur B, et al. Age effect on efficacy and side effects of two sedation and analgesia protocols on patients going through cardioversion: a randomized clinical trial. Acad Emerg Med 2006;13(5):493–9.
77. Choi SD, Spaulding BC, Gross JB, et al. Comparison of the ventilatory effects of etomidate and methohexital. Anesthesiology 1985;62(4):442–7.
78. Kolenda H, Gremmelt A, Rading S, et al. Ketamine for analgosedative therapy in intensive care treatment of head-injured patients. Acta Neurochir (Wien) 1996; 138(10):1193–9.
79. Green SM, Krauss B. The semantics of ketamine. Ann Emerg Med 2000;36(5): 480–2.
80. Erstad BL, Patanwala AE. Ketamine for analgosedation in critically ill patients. J Crit Care 2016;35:145–9.
81. Kirkbride DA, Parker JL, Williams GD, et al. Induction of anesthesia in the elderly ambulatory patient: a double-blinded comparison of propofol and sevoflurane. Anesth Analg 2001;93(5):1185–7.
82. John AD, Sieber FE. Age associated issues: geriatrics. Anesthesiol Clin North America 2004;22(1):45–58.
83. Kazama T, Ikeda K, Morita K, et al. Comparison of the effect-site k(eO)s of propofol for blood pressure and EEG bispectral index in elderly and younger patients. Anesthesiology 1999;90(6):1517–27.
84. Kettler D, Sonntag H, Donath U, et al. Haemodynamics, myocardial mechanics, oxygen requirement and oxygenation of the human heart during induction of anaesthesia with etomidate (author's transl). Anaesthesist 1974;23(3):116–21 [in German].
85. Heikkila H, Jalonen J, Arola M, et al. Midazolam as adjunct to high-dose fentanyl anaesthesia for coronary artery bypass grafting operation. Acta Anaesthesiol Scand 1984;28(6):683–9.
86. Reves JG. Valium-fentanyl interaction, in common problems in cardiac anaesthesia. Chicago: Mosby, Incorporated; 1987. p. 356.
87. Windsor JP, Sherry K, Feneck RO, et al. Sufentanil and nitrous oxide anaesthesia for cardiac surgery. Br J Anaesth 1988;61(6):662–8.
88. Idvall J, Ahlgren I, Aronsen KR, et al. Ketamine infusions: pharmacokinetics and clinical effects. Br J Anaesth 1979;51(12):1167–73.
89. Chrysostomou C, Schmitt CG. Dexmedetomidine: sedation, analgesia and beyond. Expert Opin Drug Metab Toxicol 2008;4(5):619–27.
90. Odar-Cederlof I, Boréus LO, Bondesson U, et al. Comparison of renal excretion of pethidine (meperidine) and its metabolites in old and young patients. Eur J Clin Pharmacol 1985;28(2):171–5.

91. Matteo RS, Schwartz AE, Ornstein E, et al. Pharmacokinetics of sufentanil in the elderly surgical patient. Can J Anaesth 1990;37(8):852–6.
92. Minto CF, Schnider TW, Egan TD, et al. Influence of age and gender on the pharmacokinetics and pharmacodynamics of remifentanil. I. Model development. Anesthesiology 1997;86(1):10–23.
93. Scott JC, Ponganis KV, Stanski DR. EEG quantitation of narcotic effect: the comparative pharmacodynamics of fentanyl and alfentanil. Anesthesiology 1985;62(3):234–41.
94. Macintyre PE, Jarvis DA. Age is the best predictor of postoperative morphine requirements. Pain 1996;64(2):357–64.
95. Polasek TM, Patel F, Jensen BP, et al. Predicted metabolic drug clearance with increasing adult age. Br J Clin Pharmacol 2013;75(4):1019–28.
96. Reves JG, Fragen RJ, Vinik HR, et al. Midazolam: pharmacology and uses. Anesthesiology 1985;62(3):310–24.
97. Shafer SL. The pharmacology of anesthetic drugs in elderly patients. Anesthesiol Clin North America 2000;18(1):1–29, v.
98. Gross JB, Zebrowski ME, Carel WD, et al. Time course of ventilatory depression after thiopental and midazolam in normal subjects and in patients with chronic obstructive pulmonary disease. Anesthesiology 1983;58(6):540–4.
99. Brogden RN, Goa KL. Flumazenil. A reappraisal of its pharmacological properties and therapeutic efficacy as a benzodiazepine antagonist. Drugs 1991; 42(6):1061–89.
100. Schnider TW, Minto CF, Gambus PL, et al. The influence of method of administration and covariates on the pharmacokinetics of propofol in adult volunteers. Anesthesiology 1998;88(5):1170–82.
101. Schuttler J, Ihmsen H. Population pharmacokinetics of propofol: a multicenter study. Anesthesiology 2000;92(3):727–38.
102. Arden JR, Holley FO, Stanski DR. Increased sensitivity to etomidate in the elderly: initial distribution versus altered brain response. Anesthesiology 1986; 65(1):19–27.
103. Bruder EA, Ball IM, Ridi S, et al. Single induction dose of etomidate versus other induction agents for endotracheal intubation in critically ill patients. Cochrane Database Syst Rev 2015;(1):CD010225.
104. Wang N, Wang XH, Lu J, et al. The effect of repeated etomidate anesthesia on adrenocortical function during a course of electroconvulsive therapy. J ECT 2011;27(4):281–5.
105. Stefansson T, Wickstrom I, Haljamae H. Hemodynamic and metabolic effects of ketamine anesthesia in the geriatric patient. Acta Anaesthesiol Scand 1982; 26(4):371–7.
106. Lee KH, Kim JY, Kim JW, et al. Influence of ketamine on early postoperative cognitive function after orthopedic surgery in elderly patients. Anesth Pain Med 2015;5(5):e28844.
107. Rascon-Martinez DM, Fresán-Orellana A, Ocharán-Hernández ME, et al. The effects of ketamine on cognitive function in elderly patients undergoing ophthalmic surgery: a pilot study. Anesth Analg 2016;122(4):969–75.
108. Schwenk ES, Viscusi ER, Buvanendran A, et al. Consensus guidelines on the use of intravenous ketamine infusions for acute pain management from the American Society of regional anesthesia and pain medicine, the American Academy of Pain Medicine, and the American Society of Anesthesiologists. Reg Anesth Pain Med 2018;43(5):456–66.

109. Iirola T, Ihmsen H, Laitio R, et al. Population pharmacokinetics of dexmedetomidine during long-term sedation in intensive care patients. Br J Anaesth 2012; 108(3):460–8.
110. Kim DJ, Kim SH, So KY, et al. Effects of dexmedetomidine on smooth emergence from anaesthesia in elderly patients undergoing orthopaedic surgery. BMC Anesthesiol 2015;15:139.
111. Ergenoglu P, Akin S, Bali C, et al. Effect of low dose dexmedetomidine premedication on propofol consumption in geriatric end stage renal disease patients. Braz J Anesthesiol 2015;65(5):326–32.
112. Kim J, Kim WO, Kim HB, et al. Adequate sedation with single-dose dexmedetomidine in patients undergoing transurethral resection of the prostate with spinal anaesthesia: a dose-response study by age group. BMC Anesthesiol 2015; 15:17.
113. Matteo RS, Ornstein E, Schwartz AE, et al. Pharmacokinetics and pharmacodynamics of rocuronium (Org 9426) in elderly surgical patients. Anesth Analg 1993;77(6):1193–7.
114. Miyazaki Y, Sunaga H, Kida K, et al. Incidence of anaphylaxis associated with sugammadex. Anesth Analg 2018;126(5):1505–8.
115. Muramatsu T, Isono S, Ishikawa T, et al. Differences of recovery from rocuronium-induced deep paralysis in response to small doses of sugammadex between elderly and nonelderly patients. Anesthesiology 2018;129(5):901–11.
116. Panhuizen IF, Gold SJ, Buerkle C, et al. Efficacy, safety and pharmacokinetics of sugammadex 4 mg kg-1 for reversal of deep neuromuscular blockade in patients with severe renal impairment. Br J Anaesth 2015;114(5):777–84.
117. Naguib M, Brull SJ, Kopman AF, et al. Consensus statement on perioperative use of neuromuscular monitoring. Anesth Analg 2018;127(1):71–80.
118. Sun GC, Hsu MC, Chia YY, et al. Effects of age and gender on intravenous midazolam premedication: a randomized double-blind study. Br J Anaesth 2008; 101(5):632–9.
119. Center for Drug Evaluation and Research: Dexmedetomidine Hydrochloride (Precedex). 2010. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/021038Orig1s017.pdf. Accessed October 9, 2018.
120. Giovannitti JA Jr, Thoms SM, Crawford JJ. Alpha-2 adrenergic receptor agonists: a review of current clinical applications. Anesth Prog 2015;62(1):31–9.
121. Hansen TG. Sedative medications outside the operating room and the pharmacology of sedatives. Curr Opin Anaesthesiol 2015;28(4):446–52.