Bruno Riou, M.D., Ph.D., Editor

Anesthesiology 2009; 110:1176–81

Perioperative Drug Therapy in Elderly Patients

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ADVANCES in modern medicine and public health have resulted in increased longevity, which in turn has resulted in more elderly patients (arbitrarily defined as aged 65 yr or older) coming to the operating room for a variety of surgical procedures. Even in the absence of comorbidities, these patients, as compared with their younger cohorts, respond differently to various perioperative physiologic trespasses and pharmacologic interventions. In this clinical commentary, we focus on the altered pharmacologic responses elderly patients have during the perioperative period. In many instances, elderly patients are more sensitive to drugs, and for the purposes of this clinical commentary, we use the word *sensitivity* in its general clinical meaning, *i.e.*, an enhanced response for a given dose of drug that might have a pharmacokinetic or pharmacodynamic explanation.

Normal Physiologic Function during Aging

As humans age, there is a general decline in organ function, although there is wide interindividual and intraindividual variability (*e.g.*, some organs might be affected more than others). Most importantly, the cardiovascular and pulmonary systems have reduced function that might impact patients' physiologic responses during surgery and anesthesia. Healthy elderly patients, however, might not manifest this decreased function unless stressed. That is, while they may have adequate function with normal activities, they have diminished reserves that prevent them from tolerating moderate or severe stress, such as major surgery and anesthesia. Chronic disease and acute exacerbation of chronic disease can further impact an elderly patient's response to perioperative stress (fig. 1).

There are numerous theories of aging, including cellular senescence (cells are unable to replicate DNA and divide normally) and oxidative stress (inability to protect against reactive metabolic molecules, *e.g.*, free radicals).[1] In addition, as humans age, protein structure is altered, and this likely accounts for physiologic changes of old age.[2] For example, blood vessel distensibility is drastically decreased in elderly patients and, combined with increased intimal thickness and endothelial dysfunction, will increase systolic blood pressure, as well as left ventricular workload. Myocardial hypertrophy, along with increased collagen content, creates a stiff left ventricle that depends on adequate preload to maintain cardiac output. This makes elderly patients much more susceptible to fluid overload.[3] In addition, blunted baroreflexes make geriatric patients less able to respond normally to hypovolemia and much more susceptible to orthostatic hypotension with drug therapy.[4] Taken together, these alterations in the cardiovascular system can make elderly patients more sensitive to fluid shifts and blood loss.

The pulmonary system also undergoes significant change during the aging process, with decreased forced expiratory volume, increased physiologic shunt, and increased closing volume. These pulmonary alterations increase the risk to elderly patients during the perioperative period.[5] For example, elderly patients are more likely to develop atelectasis, cough poorly, and develop pneumonia. Hypoxemia is also more likely in these patients.

Elderly patients, compared with younger ones, have increased adipose tissue, decreased muscle mass, and decreased total body water (fig. 2 and table 1). Renal function decreases over time, and this is manifested as decreased glomerular filtration rate and impaired secretion. Creatinine clearance, which depends on the glomerular filtration rate, can be estimated from the Cockroft–Gault formula:

$$\text{Creatinine clearance} = \frac{(140 - \text{age}) \cdot \text{Weight (kg)} \cdot (0.85 \text{ if female})}{72 \cdot \text{Serum Creatinine (mg/ml)}}$$

Changes in glomerular filtration rate are variable, with some elderly patients having little change over time and others having a marked decrease. Because of decreased muscle mass, serum creatinine is usually in the normal clinical range despite the lower glomerular filtration rate. All of these factors can impact how the elderly body handles drugs. Added to this are changes in protein

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Received from the Department of Anesthesiology and Pain Medicine, University of California, Davis, California. Submitted for publication June 20, 2008. Accepted for publication December 11, 2008. Support was provided solely from institutional and/or departmental sources.

The tables and figures in this article have been prepared by Dimitri Karetnikov, 7 Tennyson Drive, Plainsboro, New Jersey 08536.

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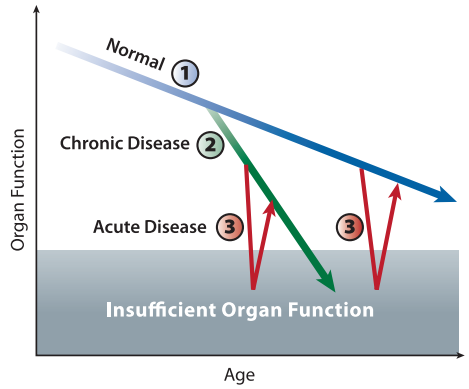

Fig. 1. Organ function declines over time in normal healthy humans, as indicated by *line 1*. Chronic disease will accelerate this decline, as noted by *line 2*. Acute disease will cause temporary rapid but reversible declines, as shown by *lines 3*. Regardless of cause, reserve function is lost when organ function declines into the *shaded area*. Adapted from Bouchon[22]; used with permission.

binding that alter free drug availability. This is important for drugs that have high protein binding.

Elderly patients are particularly vulnerable to delirium and cognitive decline in the postoperative period, and these complications are associated with increased mortality.[6] For example, the incidences of postoperative cognitive dysfunction at discharge and at 3 months after discharge are 41% and 13%, respectively, in elderly patients.[6] Preoperative memory complaints could signal early dementia and should be evaluated. Although the etiology of these serious complications is unclear, there are several potential risk factors, including advanced age, lower educational level, and history of cerebral stroke.[6] It behooves the anesthesiologist to minimize any possible contribution of excessive drug exposure to these outcomes.

Pharmacokinetics

The aging process will affect the pharmacokinetics and pharmacodynamics of many drugs used before, during,

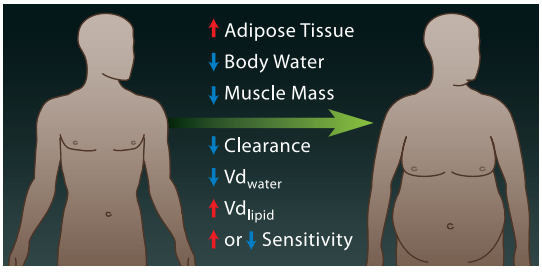

Fig. 2. Compared with young patients, elderly patients tend to have more adipose tissue, decreased body water, and less muscle mass. These changes will cause water-soluble drugs to have decreased volume of distribution (Vd_{water}), whereas lipid-soluble drugs may have increased volume of distribution (Vd_{lipid}). Clearance for most drugs is decreased in the elderly. Drug sensitivity (especially to anesthetics) is usually increased in elderly patients but may be decreased for other drugs, such as β blockers.

Table 1. Age-related Changes in Physiological Parameters

Variable	Percentage Change Elderly *vs.* Young
Body water	↓15
Lean body mass	↓35
Body fat	↑50 (women) ↑100 (men)
Serum albumin	↓20
Kidney weight	↓20
Hepatic blood flow	↓40

These are average changes and do not reflect individual variability which might be marked, *e.g.*, for kidney function. Young patients defined as 20-30 yr, elderly patients 60-80 yr.

Adapted with permission from the author (Katzung) and publisher (McGraw-Hill) from Katzung BG: Special aspects of geriatric pharmacology (chapter 61). In Katzung BG (editor): Basic and Clinical Pharmacology, 10th edition; 2007. Available at http://www.accessmedicine.com/content.aspx?aID=2512888. Accessed December 1, 2008.

and after surgery. Pharmacokinetics is often thought of as "what the body does to the drug": The drug will be distributed to blood and various tissues and will be metabolized, degraded, or secreted, thus decreasing the drug concentration over time. Pharmacodynamics is "what the drug does to the body": This is the set of pharmacologic actions produced by the drug, both desired and undesired. In general, elderly patients will be sensitive to drugs because of changes in pharmacokinetics that lead to higher concentrations for a given dose, because of pharmacodynamic changes (*i.e.*, increased sensitivity for a given drug concentration), or because of both.

For a given drug dose, the plasma concentration and the volume of distribution of a drug are inversely related. Total body water decreases as we age, and the use of diuretics exacerbates this change. Therefore, hydrophilic drugs have a smaller volume of distribution and, for a given dose, a higher plasma concentration. This will generate a greater pharmacologic effect. Morphine, for example, has a volume of distribution in the elderly that is only half of that in younger patients. Ultimately, however, the effect of a drug will depend in great part on the volume of distribution at the effect site (*i.e.*, the site where the drug exerts its desired action).

On the other hand, with the increase of body fat, the volume of distribution of lipid soluble drugs increases. This retards their elimination, as occurs with diazepam—its elimination half-life is increased severalfold in the elderly. Although this prolonged half-life might not be important after a single dose of diazepam, it would have a more significant impact with repeated dosing.

Most anesthetic drugs are, to one extent or another, protein bound. Albumin is decreased by up to 20% in the elderly, and perhaps more in the setting of poor nutri-

tion. Propofol is highly protein bound, and even modestly decreased albumin levels might affect free-drug concentrations of propofol.

Hepatic Metabolism

The size and blood flow to the liver are both reduced with aging. Liver weight remains stable (approximately 2.5% of total body weight) during much of adulthood. Past age 50 yr, however, there is a steady decline in liver weight such that at age 90 yr the liver comprises only 1.6% of body weight. Likewise, hepatic blood flow slowly decreases (0.3–1.5% per year), and between ages 25 and 65 yr there is a 40% decrease in hepatic blood flow.[7]

The liver eliminates drugs through phase I and phase II metabolism. Phase I involves drug oxidation, reduction, and hydrolysis and is catalyzed primarily by the cytochrome P450 system. Whether phase I activity is reduced with age is unclear. Other factors (*e.g.*, smoking, sedentary lifestyle, diet) might have a greater impact than age.[8] Regardless of the cause, anesthesiologists should consider the possibility that phase I metabolism is reduced in elderly patients. Phase II metabolism involves acetylation and conjugation. Most studies indicate that phase II metabolism is not affected by age.

High extraction drugs are those that are essentially "cleared" as they pass through the liver, whereas low extraction drugs are those whose concentration is little changed after passage through the liver. High extraction drugs are dependent on blood flow and are termed *flow limited* in their clearance. Low extraction drugs depend on the intrinsic clearance (liver size, total enzyme capacity) of the liver and are termed *capacity limited*. Although intrinsic clearance of conjugated agents might be unchanged by age, clearance of high extraction drugs (*e.g.*, ketamine, flumazenil, morphine, fentanyl, sufentanil, lidocaine) are directly related to liver blood flow. The clearance of these drugs decreases 30–40% in older patients, the same as the decrease in hepatic blood flow.[9] Intrinsic clearance of low extraction drugs would be assumed to be related to the decrease of total liver size seen in the elderly, but, in fact, age and the clearance of low extraction drugs seem to be unrelated. One possible explanation is that decreased albumin results in an increased unbound fraction of drug, which in turn opposes the effect of reduced hepatic metabolism.[9]

Renal Elimination

As humans age, kidney function declines, in part because of advancing glomerulosclerosis. As glomeruli become less functional and decrease in number, glomerular filtration rate decreases. In addition, renal blood flow decreases with age. These factors lead to a 25–50% reduction in glomerular filtration rate from age 20 yr to age 90 yr. Therefore, the clearance of drugs primarily eliminated by the kidneys can be expected to be decreased in elderly patients. In the absence of measured creatinine clearance, clinicians can evaluate the impact of these changes by estimating the creatinine clearance, as noted in the section Normal Physiologic Function during Aging.

All drugs, including anesthetic drugs, will undergo glomerular filtration to one extent or another. Lipid-soluble drugs (which include most anesthetic drugs and anesthetic adjuvants) will be reabsorbed in the tubules, whereas water-soluble metabolites will be excreted. Active metabolites (*e.g.*, morphine-6-glucuronide), as well as water-soluble drugs (including some muscle relaxants), can depend on the kidneys for elimination. Therefore, diminished renal function can impact the action of these drugs.

Pharmacodynamics

Aside from its concentration at the site of action, the magnitude of a drug effect depends on the number of receptors at the target site, signal transduction (ability to respond to receptor stimulation), and homeostatic processes that tend to preserve the normal function. Pharmacodynamics has not been as extensively studied in the geriatric population as pharmacokinetics. Sensitivity to drugs may increase or decrease with age. For example, older patients seem to be more sensitive to benzodiazepines even when pharmacokinetic differences are taken into consideration. Age-dependent changes in the γ-aminobutyric acid type A receptor (in number and in subunit composition) have been shown[10] and may be responsible for the increased sensitivity. Elderly patients, however, may also be less sensitive to drugs used in the perioperative period. For example, the geriatric population is less sensitive to β-adrenergic agonists and antagonists (*e.g.*, isoproterenol, propranolol). Decreased receptor number and/or affinity are likely, along with alterations in cellular response. Delayed homeostatic processes might also be responsible for the increased cardiovascular sensitivity to anesthetic drugs. That is, an anesthetic drug (such as propofol) can cause hypotension, and diminished autonomic baroreflexes in elderly patients can retard the expected physiologic response to hypotension, *e.g.*, increased heart rate and contractility.

Anesthetic Drugs

Inhaled anesthetic requirements are usually described in terms of the minimum alveolar concentration (MAC) that prevents movement in response to noxious stimulation. Other endpoints, however, are part of achieving general anesthesia, including unconsciousness. MAC_{awake} describes the anesthetic requirements to produce unconsciousness, *i.e.*, when patients no longer respond to

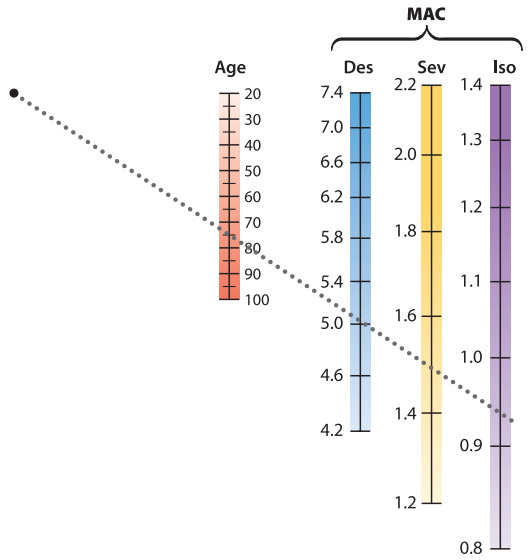

Fig. 3. Normogram for minimum alveolar concentration (MAC) as a function of age. The MACs for desflurane (Des), sevoflurane (Sev), and Isoflurane (Iso) can be determined by placing a ruler on the *dot* at left and drawing a line through the age of the patient. Where the line crosses the respective MAC normogram line yields the MAC value for that age. The *dotted line* shows an example for MAC in a 75-yr-old patient. As an approximation, MAC_{awake} (the concentration that produces unconsciousness in 50% of patients) can be determined by dividing the MAC by 3. The normograms are based on the formula: MAC fraction = $1.32 \cdot 10^{-0.00303 \cdot age}$, where MAC is the MAC fraction based on 1 MAC = MAC at age 40 yr. We assumed MAC at age 40 yr for desflurane, sevoflurane, and isoflurane to be 6.45, 1.9, and 1.2 vol%, respectively. Data and formula are from Eger.[11]

commands; it is generally around 0.33 MAC, although MAC_{awake} for halothane seems to be higher compared with the newer anesthetics. Both MAC and MAC_{awake} decrease with age, and the declines are similar.[11] If we assume that 1 MAC is at age 40 yr, MAC declines 0.6% for each year above 40 yr (fig. 3). The reasons for this decline are not obvious, except in the general sense that age affects nervous system function, whether by altered synaptic function (presynaptic) or altered neuronal function (postsynaptic). For example, dopaminergic and cholinergic neurotransmitter systems are altered during aging, and free-radical formation is age dependent. Cerebral atrophy occurs as people age, as do vascular changes and plaques. Whether these are part of normal aging or signify some underlying pathology is not yet clear. Because anesthetic-induced immobility likely occurs by an action in spinal cord, presumably the changes noted above might also occur to some extent in the spinal cord. In any case, it is not clear why anesthetic sensitivity increases with age.

Elderly patients are also more sensitive to injectable anesthetic and sedative drugs, such as thiopental, propofol, and midazolam (table 2). This increased sensitivity is related to altered pharmacokinetics, pharmacodynamics, or both. For example, elderly patients are more sensitive to etomidate, but this is due to a decreased volume of distribution, which results in a greater plasma concentration for a given dose; brain sensitivity is unchanged by aging, because at equal plasma concentrations, young and older patients have similar electroencephalographic effects.[12] The same is true for thiopental[13]; however, elderly patients are more sensitive to propofol for both pharmacokinetic and pharmacodynamic reasons.[14] Elderly patients have decreased clearance and have increased brain sensitivity to propofol. Both etomidate and propofol act at the γ-aminobutyric acid type A receptor, and it is peculiar that elderly patients have increased brain sensitivity to propofol but not to etomidate. For these reasons, we recommend that bolus injections of induction drugs (*e.g.*, propofol, thiopental, etomidate) be given over 30 s to avoid side effects such as hypotension.

Table 2. Suggested Intravenous Drug Doses

	Drugs	Young Patient	Elderly Patient
Sedative/Hypnotics	Midazolam	0.05 mg/kg	0.02 mg/kg
	Propofol	2-2.5 mg/ kg	1-2 mg/kg
	Maintenance:	**100-200 μg/kg/min**	**50-100 μg/kg/min**
	Ketamine	0.5-2mg/kg	0.3-1.5mg/kg
	Etomidate	0.2-0.3 mg/kg	0.1-0.2mg/kg
	Thiopental	3-5 mg/kg	1.5-3 mg/kg
Opiates	Fentanyl	1-2 μg/kg	0.5-1 μg/kg
	Morphine	0.03-0.06 mg/kg	0.02-0.03 mg/kg
	Sufentanil	0.5-10 μg/kg	0.25-5 μg/kg
	Remifentanil	Bolus: 0.1 μg/kg	0.05 μg/kg
	Maintenance:	**0.5-2 μg/kg/min**	**0.3-1.5 μg/kg/min**
Neuromuscular Blocking Drugs	Succinylcholine	0.5-1.0 mg/kg	0.5-1.0 mg/kg
	Rocuronium	0.1-0.6 mg/kg	0.05-0.4 mg/kg
	Vecuronium	0.02-0.06 mg/kg	0.01-0.04 mg/kg
	Pancuronium	0.02-0.1 mg/kg	0.01-0.05 mg/kg
	Cisatracurium	0.05-0.2 mg/kg	0.05-0.2 mg/kg
	Atracurium	0.2-0.5 mg/kg	0.2-0.5 mg/kg
	Doxacurium	0.01-0.03 mg/kg	0.005-0.03 mg/kg

The drug doses listed are intended to be guides and must be adjusted according to the clinical situation and needs of each patient. In general, most of the drug doses should be decreased 30-50% in elderly patients. There are some exceptions, such as some of the neuromuscular blocking drugs. Except for succinylcholine, the lower dose for each of the neuromuscular blocking drugs is for maintenance during anesthesia while the higher dose is for intubating conditions. The clinician should consider administering maintenance doses of the neuromuscular drugs less frequently. Young patients are assumed to be around 30 yr old, while elderly patients are greater than 70 yr old.

Cardiovascular Drugs

β Blockers are being increasingly used in elderly patients for ischemic heart disease and chronic heart failure. In addition, perioperative β blockade is often recommended for moderate- and high-risk patients undergoing noncardiac surgery. Pharmacokinetic and pharmacodynamic changes have been reported in the elderly for some β blockers, such as propranolol, atenolol, and metoprolol.[15] In general, the half-life is prolonged and clearance is decreased, although metoprolol is an exception, with no change in these parameters. As previously noted, elderly patients can be less sensitive to some β blockers because of down-regulation of adrenergic receptors. Because esmolol has such a short half-life, any changes in clearance are not likely to be clinically significant. Furthermore, these drugs are titrated to effect (*e.g.*, heart rate) so error in dosing can be minimized.

Many class 1 drugs (such as lidocaine) require reduced intravenous dosing because of decreased clearance and a prolonged half-life[15] (although when used for local anesthesia, the lidocaine dose need not be reduced). Likewise, some calcium channel blockers (diltiazem, nifedipine, verapamil) that undergo hepatic elimination have prolonged effects in the elderly, and reduced dosing is advised.

Digoxin is primarily excreted by the kidney and thus has a prolonged half-life in the elderly. That, along with a deceased volume of distribution, warrants decreased doses in geriatric patients. Other inotropic and vasoactive drugs (*e.g.*, dopamine, dobutamine) undergo elimination in a variety of organs and sites (hepatic, renal, plasma, other tissues) that might have reduced function in older patients. As with β blockers, these drugs are titrated to effect, so overdosing should be minimal.

Opioids

Fentanyl is commonly used perioperatively, and its rapidity of action is due in part to its high lipid solubility. Fentanyl is highly extracted by the liver, and therefore, its clearance should depend on liver blood flow; however, pharmacokinetic studies have not conclusively shown that age significantly impacts fentanyl plasma concentrations. Notwithstanding the pharmacokinetic issues, aging decreases fentanyl dosing requirements. Scott and Stanski[16] found that there is a 50% decrease in dosage requirement between the ages of 20 and 89 yr. Pharmacokinetic parameters were generally unchanged implying that there is a pharmacodynamic basis for this reduced fentanyl requirement. The pharmacologic actions of sufentanil and alfentanil are similarly affected by aging, with an approximate 50% increase in sensitivity in elderly patients. Therefore, when using these three potent drugs, clinicians should consider reducing doses by up to 50% when taking care of geriatric patients. Finally, the increased sensitivity to fentanyl and benzodiazepines, along with the synergy between the two drugs, can result in severe hypoventilation in spontaneously breathing patients.

Remifentanil is rapidly degraded by tissue and blood esterases, which results in a short duration of action (on the order of several minutes). These esterases decrease with aging and is associated with an approximately 30% decline in remifentanil clearance between ages 20 and 80 yr,[17] although this has little clinical significance given the drug's rapid metabolism. The kidney and liver have little impact on the clearance of remifentanil. The volume of distribution is reduced approximately 20% in the elderly population; hence, higher peak concentrations occur after remifentanil administration.[17] Bolus injection of remifentanil, especially large doses, can lead to severe hypotension and bradycardia, so clinicians must be careful when administering this drug to elderly patients. Elderly patients are more sensitive to the hypnotic effects of remifentanil. The plasma concentration of remifentanil required to produce electroencephalographic depression is reduced by 50% when comparing a young patient with an older patient.

Morphine's volume of distribution in older patients is decreased by 50% compared with that observed in young patients.[18] Plasma clearance is decreased. In addition, elimination of morphine's active metabolites, morphine-3- and morphine-6-glucuronide, is decreased because of decreased glomerular filtration. Sensitivity to morphine can at least be partially due to its altered pharmacokinetics, although it is unclear whether there are any pharmacodynamic causes of increased morphine sensitivity in the elderly. In any case, clinicians should reduce the initial dose of morphine. Patient-controlled analgesia using morphine can be provided to elderly patients as long as basal rates and bolus doses are decreased to adjust for pharmacodynamic changes (if any) and pharmacokinetic changes.

Muscle Relaxants

As with other drugs, muscle relaxant pharmacology is usually described in terms of onset of action, dose–response, and duration of action. In general, muscle relaxants in elderly patients have a prolonged onset of action, primarily because of deceased muscle blood flow and cardiac output associated with aging.[19] Because elderly patients have decreased body water and many of the muscle relaxants are highly water soluble (because of high ionization), the dose–response in the older patient can be greater than that in younger patients. Muscle relaxants that are eliminated by hepatic or renal excretion (*e.g.*, vecuronium, rocuronium) will often have prolonged durations of action, whereas relaxants that are

eliminated by other means (*e.g.*, cisatracurium) might not have appreciably long durations of action. The recovery indices (time from 75% block to 25% block) are increased by as much as 200% for neuromuscular blocking drugs. For example, the recovery index for vecuronium is 15 min in young patients compared with nearly 50 min in elderly patients; the rocuronium recovery index goes from 13 to 22 min, whereas that of pancuronium increases from approximately 40 to 60 min. Finally, all clinical changes in neuromuscular blocking agents have been explained by pharmacokinetic and not pharmacodynamic alterations.

Pancuronium is the prototypical steroid-based muscle relaxant, and its elimination is mostly by renal excretion (up to 70%). Hence, because renal blood flow and glomerular filtration are often reduced in the elderly, clinicians can expect pancuronium's duration of action to be prolonged. Vecuronium, which is structurally similar to pancuronium, is eliminated in bile (with minimal metabolic breakdown) and urine. The age-related changes in hepatic blood flow and capacity, along with decreased renal function, reduce vecuronium clearance (by 30–50%) in elderly patients. Rocuronium pharmacology in geriatric patients is similar to that of vecuronium in that elimination in bile and urine are the predominant modes of clearance. Therefore, rocuronium's duration of action is prolonged in elderly patients. Unlike vecuronium, however, no active metabolites are produced. In summary, clinicians can expect the steroid-based muscle relaxants to have a longer duration of action in the elderly population as compared with that observed in younger patients. This factor, combined with possible decreased volumes of distribution, warrants less frequent (and perhaps lower) maintenance doses of these drugs in the older patient.

The benzylisoquinolinium drug class includes atracurium, mivacurium, cisatracurium, and doxacurium. Some of these drugs (*e.g.*, atracurium, mivacurium) consist of numerous isomers. In fact, cisatracurium is one of the isomers of atracurium. Mivacurium is degraded by plasma pseudocholinesterases.

Hofmann elimination and ester hydrolysis account for the breakdown of atracurium and cisatracurium. The majority of cisatracurium (around 80%) is degraded by these pathways, although atracurium clearance also depends on hepatic metabolism. The durations of action of atracurium and mivacurium are increased by aging,[20] while there do not seem to be any major age-related changes in the recovery profile of cisatracurium.

The depolarizing relaxant succinylcholine is rapidly metabolized by pseudocholinesterases, and although these enzymes might be altered by aging, this is probably of little clinical significance. Onset time of succinylcholine, however, is prolonged in elderly patients, presumably because of decreased muscle blood flow and cardiac output as noted above.[21]

Conclusions

The geriatric population is a growing segment of our population; they are a heterogeneous group and, compared with younger patients, they respond differently to anesthetic medications. Increased body fat and decreased total body water and muscle mass account for many of the pharmacokinetic changes. Changes in hepatic and renal function are responsible for altered clearances of drugs. Increased sensitivity is seen with many drugs, so starting with small dosages and titrating to effect (start low and go slow) is advised when taking care of elderly patients during the perioperative period.

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