Pharmacology for the Geriatric Surgical Patient

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KEYWORDS

• Geriatrics • Surgery • Pharmacology • Adverse drug reactions

KEY POINTS

- Physical changes with age alter how medications act and are metabolized by the body.
- The elderly are at increased risk of experiencing an adverse effect of medications, especially during the postoperative period when additional medications are added to their regimen.
- All medications used in the elderly should be dose adjusted to account for altered pharmacokinetics and should be titrated to the lowest effective dose for the shortest appropriate duration.

INTRODUCTION

The elderly make up a significant proportion of the population in the United States. In 2011, adults older than 65 years made up 13.3% of the United States population or approximately 41.1 million, and those over the age of 85 comprised about 5.7 million people. The elderly are also living healthier lives, with 44% of noninstitutionalized elderly describing their health as very good or excellent (http://www.aoa.gov/Aging_Statistics/. Accessed 3/13/2014.)

Unfortunately, the elderly are at increased risk of experiencing an adverse drug reaction (ADR). ADRs may account for up to 24% of hospitalizations in the elderly. Approximately 1 in 6 elderly patients will experience an ADR during admission to hospital.[1,2] ADRs in the elderly often present in an atypical manner and are nonspecific. A single ADR can increase a patient's length of stay in hospital by an average of 6.2 days.[3]

Many ADRs are preventable, as they are based on the known mechanism of action and/or predictable decreased clearance of the medication, withdrawal of a chronic

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medication, or a drug-drug interaction.[1] Awareness of common physiologic changes and common drug-drug interactions seen in the elderly may help prevent ADRs in geriatric surgical patients (**Box 1**).

CHANGES IN PHARMACOKINETICS AND PHARMACODYNAMICS

Aging is not a single process, so as individuals age their interindividual variability accumulates. This variation creates differences in response to physiologic stress. The ease with which elderly patients tolerate surgery is related to their specific aging process. In general, the elderly experience many physiologic changes that affect their ability to metabolize and use medications (**Tables 1** and **2**). The frail elderly require even more caution when dosing and using medications.

Absorption and Bioavailability

Saliva production and gastric acid secretion are thought to be reduced as a result of aging. Although this theoretically could cause less drug to be available for absorption because of changes in ionization, in clinical practice this change seems to have little effect on medications used in the geriatric patient. Alternatively, these changes may be more frequent in frail patients and do not apply to healthy older patients who lack comorbid conditions.[4]

Oral bioavailability is not only determined by the amount of drug present in the gastrointestinal (GI) tract but also whether the absorbed drug undergoes first-pass hepatic metabolism before systemic distribution. First-pass metabolism reduces the amount of drug reaching the systemic circulation, thus reducing bioavailability. This first-pass metabolism may be impaired by decreased blood flow to the liver or by decreased activity of hepatic enzymes, leading to a decreased amount of drug extracted.[5] In turn this may lead to higher serum concentrations of certain medications (eg, propranolol and labetalol).[4]

Distribution

Body composition changes over time. As the body ages, total body fat increases at the expense of lean body mass and total body water. These changes lead to a smaller volume of distribution and, consequently, higher drug concentration for hydrophilic medications such as digoxin, but larger volumes of distribution for lipophilic medications such as lidocaine, phenytoin, and benzodiazepines.[1,4,5] The distribution of these medications into the adipose tissue may lead to a delayed effect of the medication.

Box 1
Common drug classes associated with adverse drug reactions

- Antibiotics
- Digoxin
- Antihyperglycemic agents
- Anticoagulants/Antithrombotics
- Diuretics
- Nonsteroidal anti-inflammatory agents

Adapted from Petrovic M, van der Camme T, Onder G. Adverse drug reactions in older people: detection and prevention. Drugs Aging 2012;29:454.

Table 1
Age-related changes that affect pharmacokinetics

Change in Elderly Patients Compared with Younger Patients	Possible Effect of Changes on Drug Concentration in the Elderly
Decreased gastric acid production	Increase or decrease depending on medication
Decreased gastric blood flow	Decreased adsorption
Decreased first-pass effect	Increased availability of active drugs; decreased availability of drugs requiring activation
Increased body fat	Decrease lipophilic medications
Decreased lean body mass/total body water	Increase hydrophilic medications
Decreased albumin	Increase unbound (active) drug
Decreased size of liver and blood flow	Increase
Glomerular filtration rate	Increase
Tubular function	Decrease

However, after the medication is discontinued it may be slowly released from the adipose stores, leading to prolonged therapeutic effects.[6]

Changes in the serum proteins, albumin and α1-acid glycoprotein, can also alter the amount of active drug in the body. The effect of alterations in protein binding is generally only observed in the frail elderly and may be more related to disease states than the aging process per se, because renal disease, liver disease, and even diabetes mellitus are known to alter drug binding. In these patients, however, toxicity may be observed for medications such as phenytoin, digoxin, and warfarin despite total drug levels being in the therapeutic range.[6] Monitoring free (nonprotein bound) drug levels should be considered in the frail elderly when possible.

Besides the chemical properties of a medication, transporter proteins such as P-glycoprotein are integral to the ability of a drug to cross the blood-brain barrier and other tissues. P-glycoprotein, like many other enzymes, seems to have decreased activity with aging. At present, however, there is no known clinical consequence of this potential decrease in activity.[5]

Table 2
Examples of pharmacodynamics changes in the elderly

Medication	Pharmacodynamic Effect	Change in Elderly
Diazepam	Sedation, postural sway	Increased
Diltiazem	Antihypertensive effects	Increased
Diphenhydramine	Postural sway	Increased
Furosemide	Diuretic response	Decreased
Heparin	Anticoagulation effects	No change
Isoproterenol	Chronotropic effects	Decreased
Phenylephrine	α-Adrenergic response	No change
Temazepam	Postural sway	Increased
Verapamil	Antihypertensive effects	Increased
Warfarin	Anticoagulant effects	Increased

Metabolism

There are clear changes in various organs as they age. The liver decreases in size as well as hepatic blood flow. This reduction in perfusion can slow the rate at which medications are delivered to the liver for metabolism. Declines in the function of the various cytochrome P450 isoenzymes that account for phase I metabolism appear in both the frail and healthy elderly. Studies to characterize the percentage decline in individual isozymes are limited by genetic differences in patients who appear to physiologically age at different rates, and other factors such as smoking status, ethnicity, and sex.[4,5] Unfortunately, at this time there are no routine clinical tests that can aid in determining the amount of liver impairment in a specific patient.

In healthy patients through 80 years of age there appears to be little decline in phase II metabolism, which is responsible for glucuronidation, acetylation, and sulfation.[4] Esterases found throughout the body in various tissues and in the plasma do not show a decline in function in healthy elderly patients, but are significantly reduced in the frail elderly and those patients having suffered hip fractures, delirium, and even pneumonia.[6]

Elimination

Aging is associated with a reduction in the number of renal glomeruli (see article by Baldea AJ, elsewhere in this issue). Despite this reduction in number, about one-third of elderly patients will maintain their glomerular filtration rate (GFR) through almost 90 years of age. In a small percentage of patients, GFR increases with age.[5,6] Declines in GFR seem to be most related to concomitant diseases, such as hypertension, chronic heart failure, and diabetes mellitus.[5] Although frailty may be related to decreasing GFR, it is as yet unknown whether it is a consequence or a cause of renal impairment.[6]

Tubular secretion and reabsorption may decrease in the elderly, although these parameters are not well characterized or assessed by current methods of estimating GFR. Decreases in renal function may also lead to alterations in liver metabolism of certain medications, as a result of either reduced gene expression or shifting of clearance from the renal system to the hepatic system.[4]

Pharmacodynamics

A drug's action in the body can be affected by the aging process. For example, the elderly have a decreased response to verapamil's effects on cardiac conduction but an increased response to its vasodilator properties. β-Adrenoceptor responsiveness is also decreased in the elderly, and seems to be related to reductions in cyclic adenosine monophosphate after receptor stimulation. α-Adrenoceptors do not appear to be affected by aging.[4]

Despite similar plasma concentration in young and elderly patients, there is greater inhibition of clotting factors in the presence of warfarin and increased sedation in the presence of diazepam.[4,6] The mechanisms for these effects are unknown at present.

PREOPERATIVE ISSUES

A complete medication history is imperative before elective surgery. The elderly take on average 2 to 5 prescription medications daily.[5] Those who are institutionalized may take closer to 7 pharmacologic agents daily. Unfortunately, this does not account for all medications that an elderly patient may be using regularly. The elderly use 3 times more over-the-counter preparations and twice the number of alternative/herbal preparations in comparison with the population in general.[2]

Medication allergies and previous ADRs should also be investigated before surgery to prevent similar drugs from being prescribed during the perioperative period. Reactions to medications should be discussed and documented to distinguish between true allergies and intolerances.

A plan should be created to address long-term medications that cannot or should not be stopped abruptly if the likelihood is that the patient will not be able to resume oral medications immediately postoperatively. Specific examples include β-blockers, antidepressants, antipsychotics, and anxiolytics. The elderly may be at increased risk of postoperative atrial fibrillation caused by age and comorbidities. The abrupt discontinuation of β-blockers can further increase the risk of postoperative atrial fibrillation.[7]

For patients on anticoagulant or antiplatelet therapy, the associated bleeding risk of the surgery should be weighed against the risk of discontinuing the agent, which is predicated on the indication for the agent. Ideally a plan should be devised jointly by the surgeon and the prescribing physician to determine the length of time to hold long-term therapy and to determine whether bridging therapy is appropriate (Table 3).

POSTOPERATIVE ISSUES

The risk of ADRs is greatest after an elderly patient's operation, owing to the introduction of new medications, including anesthetics, analgesics, antiemetics, and chemoprophylaxis for deep venous thrombosis. In addition, fluid resuscitation can significantly increase the volume of distribution of medications, leading to underdosing. On the other hand, postoperative renal or hepatic dysfunction can decrease metabolism, leading to toxicity.

Medications added to treat postoperative complications, such as atrial fibrillation, delirium, or infections, can further increase risk. When a patient is taking only 2 medications concurrently, the estimated risk of an ADR is 13%, but this risk increases to

Table 3
Potential management of newer anticoagulants before surgery

Drug	Renal Function	Low Bleeding Risk Surgery	High Bleeding Risk Surgery
Dabigatran 150 mg BID	Normal to mild impairment (CrCl >50 mL/min)	Skip 2 doses	Skip 4 doses
Dabigatran 150 mg BID	Moderate impairment (CrCl 30–50 mL/min)	Skip 4 doses	Skip 6–8 doses
Rivaroxaban 20 mg QD	Normal to mild impairment (>50 mL/min)	Skip 1 dose	Skip 2 doses
Rivaroxaban 15 mg QD	Moderate impairment (30–50 mL/min)	Skip 1 dose	Skip 2 doses
Rivaroxaban 15 mg QD	Severe impairment (CrCl 15–29 mL/min)	Skip 2 doses	Skip 3 doses
Apixaban 5 mg BID	Normal or mild impairment (>50 mL/min)	Skip 2 doses	Skip 4 doses
Apixaban 5 mg BID	Moderate impairment (30–50 mL/min)	Skip 4 doses	Skip 6 doses

Abbreviations: BID, twice daily; CrCl, creatinine clearance; QD, every day.

Adapted from Spyropoulos AC, Douketis JD. How I treat anticoagulated patients undergoing an elective procedure or surgery. Blood 2012;120:2959.

82% with 7 medications.[1] Each medication added may have its own adverse effects and/or may interact with a medication that the patient is already receiving.

In the elderly it is important to not overtreat. The worst scenario occurs when additional medications are used to treat adverse reactions from other medications, leading to an iatrogenic cascade. It is crucial to investigate why the patient has a new symptom.[2]

Pain

Pain is subjective and completely known only to the patient experiencing it. Pain assessment in the elderly is complicated by cognitive impairment, communication difficulties, and cultural differences. Pain-intensity scales can be used in most patients without severe cognitive impairment, but may require more patience and time to complete with the elderly patient. Physical cues that a patient is in pain may be present, but if a patient has a chronic pain syndrome, common clinical signs such as tachycardia and hypertension may be absent.[8] For patients who are impaired, family input can be helpful in some circumstances.

Multimodal therapy may be especially important in the elderly (**Table 4**). A combination of weaker and stronger analgesics along with adjuvant and nonpharmacologic treatments may decrease the risk of severe adverse reactions.[8]

Delirium is frequently considered an adverse effect of opioid medications. In some studies, the risk of delirium was increased in patients receiving opioids in comparison with those who did not. By contrast, other studies have suggested that underdosing of opiates increased the risk of delirium. Patients with severe pain appear to have a significantly increased risk of delirium. Adequate treatment of pain and appropriate selection of medication are critical for decreasing the risk of delirium in the elderly.[9]

Table 4
Precautions for the elderly taking pain medications

Drug	Precaution	Recommendation
Acetaminophen	Metabolism maintained in healthy elderly; caution in frail, malnourished, dehydrated, and high alcohol consumption	May benefit most from scheduled doses; maintain strict 4 g limit in 24 h; consider lower doses (2–3 g max/24 h) in high-risk groups
NSAIDs	Elderly seem to be at higher risk of GI bleeding, renal dysfunction, and prolonged half-lives of some agents	Short half-life agents such as ibuprofen or diclofenac, given at the lowest effective dose for a short duration, may decrease risk but close monitoring required
Tramadol	Associated with delirium, seizures, dizziness, nausea/vomiting Requires renal dose adjustment and activation by the liver to its active form	May have fewer respiratory and GI adverse effects but dose adjustments required in renal dysfunction
Opioids	Most opioids are metabolized in the liver and excreted renally Increased risk of falls with injury when opioids are initiated	Use of short-acting agents that can quickly be titrated to adequate pain control may decrease delirium

Abbreviations: GI, gastrointestinal; NSAIDs, nonsteroidal anti-inflammatory drugs.

The ideal pain medication in the elderly would have a predictable half-life, no active metabolites, and be easily titratable. Agents such as morphine and meperidine have active metabolites and should be used sparingly in elderly patients, especially those with renal impairment. Oxycodone, hydromorphone, and fentanyl are generally recommended, even in patients with impaired renal function.[8,9]

Tapentadol, meperidine, tramadol, fentanyl, and oxycodone have the potential to interact with serotonin reuptake inhibitors, and potentially lead to serotonin syndrome.[10] Codeine and tramadol require activation by the liver, which may be impaired because of drug interactions or frailty.[9]

The elderly should also be monitored for constipation, nausea, and dizziness while receiving pain medications. A bowel regimen should include a stimulant or osmotic laxative, such as senna or polyethylene glycol, and should be started as soon as possible after initiation of opioid therapy.

Adjuvant therapies such as gabapentin, pregabalin, ketamine, and topical agents (eg, lidocaine and capsaicin) may be beneficial in the postoperative period for pain control, but have not been studied in the elderly.[8] If adjunctive therapies are used, elderly patients should be started on a low dose that can be titrated up slowly, keeping the potential for decreased end-organ function in mind.

Nausea

Postoperative nausea and vomiting can be difficult to control in the elderly, owing to the risk of multiple ADRs with common antiemetics. Ondansetron and other serotonin receptor blockers may have fewer ADRs but should still be used cautiously in patients at risk for QTc prolongation. Use of other agents such as promethazine and prochlorperazine should be limited, owing to the level of sedation they can induce. Metoclopramide should not be used in patients with Parkinson disease because of its drug-disease interaction.[11] New agents such as aprepitant are limited by expense and multiple drug interactions. Alvimopan, which is indicated to speed the return of GI function postoperatively, is limited by its potential increased risk for myocardial infarction.

Atrial Fibrillation

The risk of atrial fibrillation increases as the body ages. The elderly may be less tolerant of tachycardia as a result of reliance on stroke volume to maintain perfusion in the setting of impaired cardiac contractility.

Unfortunately, the elderly are also not very tolerant of antiarrhythmic therapy. A post hoc analysis of the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial that selected participants who were 70 to 80 years of age compared rate-control with rhythm-control therapy for atrial fibrillation. All-cause mortality was significantly lower in the rate-control group than the rhythm-control group (18% vs 23%, $P = .01$) after a median of 3.4 years of follow-up. There was no change in cardiovascular mortality, but a significant decrease in noncardiovascular mortality in the rate-control group (8% vs 12%, $P = .002$). There was also a decrease in all-cause hospitalization in the rate-control group (61% vs 68%, $P<.001$).[12] The target heart rate in this study was less than 80 beats/min at rest. A subsequent study in which the median age was 68 years found that targeting a heart rate of less than 110 beats/min instead of less than 80 beats/min decreased the composite of cardiovascular death, hospitalization due to heart failure, stroke, major bleeding, syncope, sustained ventricular tachycardia, cardiac arrest, and life-threatening adverse medication effects.[13] Both studies used β-blockers as first-line agents for rate control. In its 2011 update to the atrial

fibrillation guidelines, the American Heart Association recommends that, in patients with an ejection fraction greater than 40% and no or acceptable symptoms, there is no benefit of targeting a heart rate less than 80 beats/min over targeting a heart rate less than 110 beats/min.[14]

β-Blockers and calcium-channel blockers are recommended as first-line therapy in the elderly to manage atrial fibrillation in the perioperative period. Sotalol may also be used, but must be adjusted for renal function. Digoxin is not recommended because of its multiple drug interactions and altered pharmacokinetics in the elderly. If digoxin is chosen, careful attention should be paid to the patient's renal function, as this will affect the volume of distribution of digoxin and increase the likelihood for toxicity.

Anticoagulation

Elderly patients may be at an increased risk of bleeding when initiated on anticoagulation. For patients requiring venous thromboembolism prophylaxis, time from surgery and renal function need to be considered before initiation. Many agents can be started in as little as 6 hours postoperatively. Multiple agents, however, are inappropriate for patients with renal impairment. Rivaroxaban, fondaparinux, and enoxaparin should be used with caution when estimated creatinine clearance is less than 30 mL/min. Enoxaparin in one study was also found to be associated with an increased risk of bleeding in those with a creatinine clearance between 30 and 50 mL/min.[15] Unfractionated heparin does not appear to be affected by age or renal function.

For patients who have been anticoagulated preoperatively, therapeutic anticoagulation should be restarted as soon as is safely possible. Some elderly patients will require dose adjustments to account for renal function and body weight. For example, the dose of apixaban should be reduced in patients weighing less than 60 kg to 2.5 mg twice daily, and fondaparinux should be decreased to 2.5 mg daily for weight less than 50 kg and 10 mg daily for those weighing greater than 100 kg. The newer oral anticoagulants, dabigatran, apixaban, and rivaroxaban, can generally be restarted 24 hours after surgery if there is a low bleeding risk, or in 48 to 72 hours if the bleeding risk is high.[16] The anticoagulant effect of these newer agents is seen within hours of the first dose, so they should not be concomitantly bridged with other anticoagulants.

SUMMARY

As the body ages, drug metabolism and drug effects change. These alterations in pharmacodynamics and pharmacokinetics place the elderly at an increased risk of experiencing an ADR. The incidence of medication-related adverse events can be decreased with careful selection of agents and appropriate dosage adjustments.

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