Pharmacotherapy 2

Geriatrics: The Aging Process in Humans

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Pharmacologic Changes Associated with Aging

- ✓ Measurements of functional capacity of most of the major organ systems show a decline beginning in young adulthood and continuing throughout life.

<u>Epidemiology of aging</u>

- ✓ The proportion of persons 65 years and older is increasing worldwide.
- ✓ In 2015, the percentage of people 65 years and older in the world was 8.5% and is projected to increase to 16.7% in 2050.

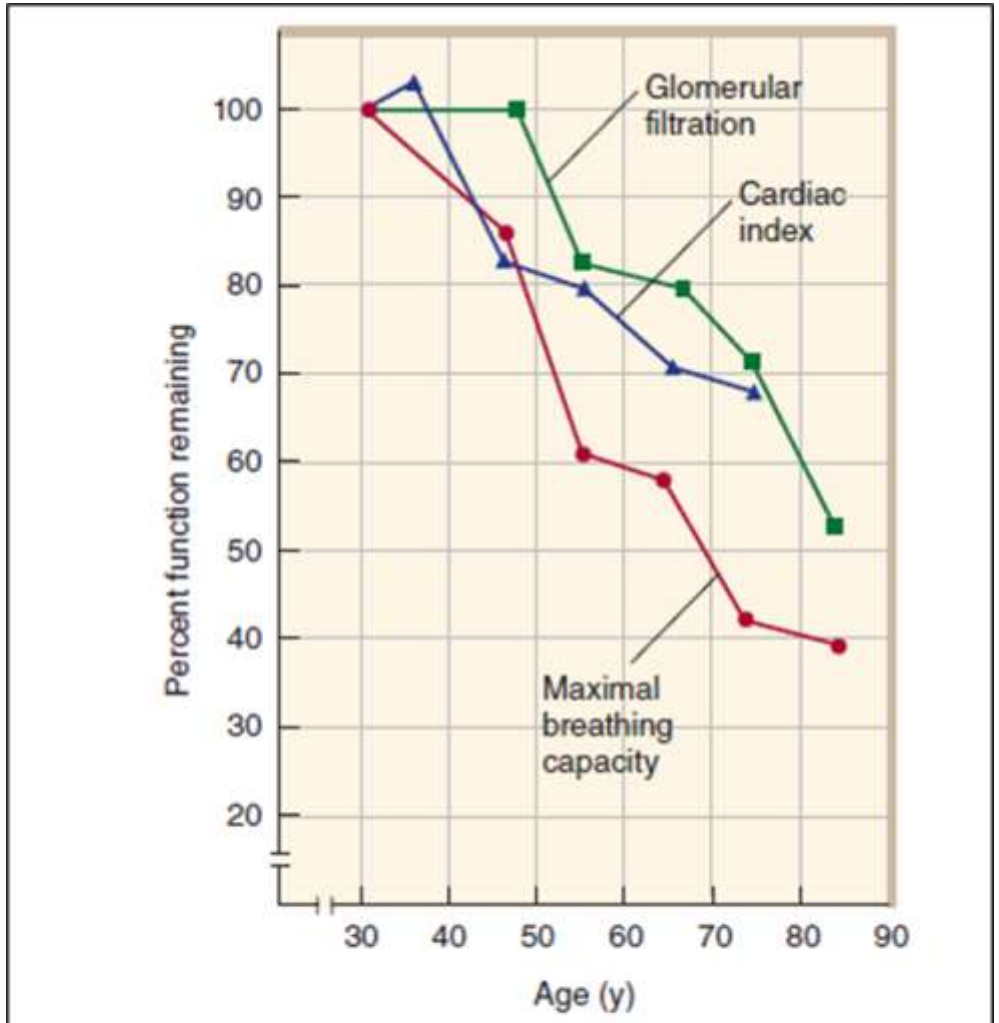

FIGURE 60–1 Effect of age on some physiologic functions.

(Adapted, with permission, from Kohn RR: *Principles of Mammalian Aging*. Copyright copy; 1978 by Prentice-Hall, Inc. Used by permission of Pearson Education, Inc.)

Age-Related Changes in Drug Pharmacokinetics

Pharmacokinetic Phase	Pharmacokinetic Parameters
Gastrointestinal absorption	Unchanged passive diffusion and no change in bioavailability for most drugs
	↓ Active transport and ↓ bioavailability for some drugs
	↓ First-pass metabolism, ↑ bioavailability for some drugs and ↓ bioavailability for some prodrugs
Distribution	↓ Volume of distribution and ↑ plasma concentration of water-soluble drugs
	↑ Volume of distribution and ↑ terminal disposition half-life ($t_{1/2}$) for lipid-soluble drugs
Hepatic metabolism	↓ Clearance and ↑ $t_{1/2}$ for some drugs with poor hepatic extraction (capacity-limited metabolism). Phase I metabolism may be affected more than Phase II.
	↓ Clearance and ↑ $t_{1/2}$ for drugs with high hepatic extraction ratios (flow-limited metabolism)
Renal excretion	↓ Clearance and ↑ $t_{1/2}$ for renally eliminated drugs and active metabolites

Data from References 29 and 30.

TABLE 60–1 Some changes related to aging that affect pharmacokinetics of drugs.

Variable	Young Adults (20–30 years)	Older Adults (60–80 years)
Body water (% of body weight)	61	53
Lean body mass (% of body weight)	19	12
Body fat (% of body weight)	26–33 (women)	38–45
	18–20 (men)	36–38
Serum albumin (g/dL)	4.7	3.8
Kidney weight (% of young adult)	100	80
Hepatic blood flow (% of young adult)	100	55–60

Pharmacokinetic Changes

- ✓ Absorption
  - Conditions associated with age may alter the rate at which some drugs are absorbed.
  - Such conditions include changes in gastric emptying, which is often slower in older persons, especially in older diabetics, and greater consumption of OTC drugs (eg, antacids and laxatives).

- ✓ Distribution
  - Compared with young adults, the elderly have reduced lean body mass, reduced body water, and increased fat as a percentage of body mass.
  - There is usually a decrease in serum albumin, which binds many drugs, especially weak acids.
  - Thus, the ratio of bound to free drug may be significantly altered.

✓ Metabolism

- The capacity of the liver to metabolize drugs declines with age for some, but not all, drugs.
- The greatest changes are in phase I reactions -those carried out by microsomal P450 systems.
- There are much smaller changes in ability of liver to carry out conjugation (phase II) rxns.
- There is a decline with age of the liver's ability to recover from injury, eg, that caused by alcohol or viral hepatitis (A history of recent liver disease in an older person should lead to caution in dosing with drugs that are cleared primarily by the liver, even after apparently complete recovery from the hepatic insult).

✓ Elimination

- A decline in Clcr (usual measure of eGFR) occurs in about two thirds of the population.
- It is important to note that this decline is not reflected in an equivalent rise in serum creatinine because the production of creatinine is also reduced as muscle mass declines with age; therefore, serum creatinine alone is not an adequate measure of renal function.
- The practical result of this change is marked prolongation of the half-life of many drugs, and the possibility of accumulation to toxic levels if dosage is not reduced in size or frequency.

Pharmacodynamic Changes

- ✓ Age-related changes in pharmacokinetics are well characterized compared to changes in pharmacodynamics.

- ✓ There is a general trend of altered drug response or increased “sensitivity” in older adults.

- ✓ Possible mechanisms that have been proposed include:
  - changes in concentrations of the drug at the receptor
  - changes in receptor numbers
  - changes in receptor affinity
  - age-related impairment of homeostatic mechanisms

- ✓ Older adults are particularly sensitive to the CNS effects of drugs. Changes in brain size and weight as well as changes in neurotransmitter systems have been reported with advancing age.

- ✓ Drugs may penetrate the CNS more easily.

- ✓ Increased sensitivity to the CNS effects of medications in older adults has been demonstrated for benzodiazepines, anesthetic agents, opioid analgesics, antipsychotics, lithium, and anticholinergic medications.

- ✓ Aging is associated with numerous changes in the structure and function of the CV system that may predispose the older adult to altered pharmacodynamic response to drugs acting on the CV system.

- ✓ Older adults are more likely to experience orthostatic hypotension as an adverse drug event.

- ✓ Age-related changes in pharmacodynamics have been reported for CCBs (increased hypotensive and bradycardic effects), beta blockers (reduced BP response), diuretics (reduced effectiveness), and warfarin (increased risk of bleeding), but not with ACEIs or ARBs.

Adverse Drug Reactions in The Elderly

- ✓ The overall incidence of ADRs in geriatric patients is estimated to be at least twice that in the younger population.
- ✓ Reasons for this high incidence include errors in prescribing on the part of the practitioners and errors in drug usage by the patient.
- ✓ Practitioner errors sometimes occur because the physician does not appreciate the importance of changes in pharmacokinetics with age and age-related diseases.
- ✓ Some errors occur because the practitioner is unaware of incompatible drugs prescribed by other practitioners for the same patient.
- ✓ Patient errors often result from use of nonprescription drugs taken without the knowledge of the physician.

Practical Aspects Of Geriatric Pharmacotherapy

- ✓ The quality of life in elderly patients can be greatly improved and life span can be prolonged by the intelligent use of drugs.

- ✓ Several practical obstacles to compliance:
  - The expense of drugs
  - Awareness of the cost of the prescription and of cheaper alternative therapies
  - Nonadherence may result from forgetfulness or confusion, especially if the patient has several prescriptions and different dosing intervals.
  - Patients may forget instructions regarding the need to complete a fixed duration of therapy when a course of anti-infective drug is being given.

- The disappearance of symptoms is often regarded as the best reason to halt drug taking, especially if the prescription was expensive.

- Nonadherence may also be deliberate. A decision not to take a drug may be based on prior experience with it (Enlisting the patient as a participant in therapeutic decisions increases the motivation to succeed).

- Some errors in drug taking are caused by physical disabilities. Arthritis, tremor, and visual problems may all contribute:

  - Liquid medications that are to be measured “by the spoonful” are especially inappropriate for patients with any type of tremor or motor disability. Use of a dosing syringe is essential in such cases.

  - Because of decreased production of saliva, older patients often have difficulty swallowing large tablets.

  - “Childproof ” containers are often “elder-proof ” if the patient has arthritis.

- Cataracts and macular degeneration occur in a large number of patients over 70. Therefore, labels on prescription bottles should be large enough for the patient with diminished vision to read or should be **color-coded** if the patient can see but can no longer read.

- Because of impaired hearing, even carefully delivered instructions regarding drug use may not be understood by the patient; written instructions may be helpful.

✓ Drug therapy has considerable potential for both helpful and harmful effects in the geriatric patient. The balance may be tipped in the right direction by adherence to a few principles:

- Take a careful drug history. The disease to be treated may be drug-induced, or drugs being taken may lead to interactions with drugs to be prescribed.

- Prescribe only for a specific and rational indication. Do not prescribe omeprazole for "dyspepsia." Expert guidelines are published regularly by national organizations and websites such as UpToDate.com.

- Define the goal of drug therapy. Then start with small doses and titrate to the response desired. Wait at least three half-lives (adjusted for age) before increasing the dose.

- Maintain a high index of suspicion regarding drug reactions and interactions. Know what other drugs the patient is taking, including OTC and botanical (herbal) drugs.

- Simplify the regimen as much as possible. When multiple drugs are prescribed, try to use drugs that can be taken at the same time of day. Whenever possible, reduce the number of drugs being taken.

Physiologic Changes with Aging

Organ System	Manifestation
Balance and gait	↓ Stride length and slower gait
	↓ Arm swing
	↑ Body sway when standing
Body composition	↓ Total body water
	↓ Lean body mass
	↑ Body fat
	↔ or ↓ Serum albumin
	↑ α_1-Acid glycoprotein (↔ or ↑ by several disease states)
Cardiovascular	↓ Cardiovascular response to stress
	↓ Baroreceptor activity leading to ↑ orthostatic hypotension
	↓ Cardiac output

Physiologic Changes with Aging

	↑ Systemic vascular resistance with loss of arterial elasticity and dysfunction of systems maintaining vascular tone
	↑ Afterload
	↓ Coronary Perfusion
Central nervous system	↓ Size of the hippocampus and frontal and temporal lobes
	↓ Number of receptors of all types and ↑ sensitivity of remaining receptors
	↓ Short-term memory, coding and retrieval, and executive function
	Altered sleep patterns
Endocrine	↓ Estrogen, testosterone, thyroid stimulating hormone, and DHEA-S levels
	Altered insulin signaling
Gastrointestinal	↓ Motility of the large intestine
	↓ Vitamin absorption by active transport mechanisms
	↓ Splanchnic blood flow

Physiologic Changes with Aging

	↓ Bowel surface area
Genitourinary	Atrophy of the vagina with decreased estrogen
	Prostatic hypertrophy with androgenic hormonal changes
	Detrusor hyperactivity may predispose to incontinence
Hepatic	↓ Hepatic size
	↓ Hepatic blood flow
	↓ Phase I (oxidation, reduction, hydrolysis) metabolism
Immune	↓ Antibody production in response to antigen
	↑ Autoimmunity
Oral	Altered dentition
	↓ Ability to taste salt, bitter, sweet, and sour
Pulmonary	↓ Respiratory muscle strength
	↓ Chest wall compliance
	↓ Arterial oxygenation and impaired carbon dioxide elimination

Physiologic Changes with Aging

	↓ Vital capacity
	↓ Maximal breathing capacity
	↑ Residual volume
Renal	↓ Glomerular filtration rate
	↓ Renal blood flow
	↓ Filtration fraction
	↓ Tubular secretory function
	↓ Renal mass
Sensory	Presbyopia (diminished ability to focus on near objects)
	↓ Night vision
	Presbycusis (high-pitch, high-frequency hearing loss))
	↓ Sensation of smell and taste
Skeletal	↓ Skeletal bone mass (osteopenia)

Physiologic Changes with Aging

	Joint stiffening due to reduced water content in tendons, ligaments, and cartilage
Skin/hair	Thinning of stratum corneum
	↓ Langerhans cells, melanocytes and mast cells
	↓ Depth and extent of the subcutaneous fat layer
	Thinning and graying of hair due to more hairs in the resting phase and shortening of the growth phase as well as changes in follicular melanocytes

Data from References 24 and 27.