

PHARMACOTHERAPY OF GERIATRIC PRACTICE

**1. Dr. Ayesha Siddiquea (Corresponding author, email -
ayeshasid6@gmail.com)**

**PG Student, Department of Pharmacology
Navodaya medical college, Raichur.
Karnataka, INDIA.**

2. Dr . Navin A. Patil

**PG Student , Department of Pharmacology
JJM Medical College , Davangere
Karnataka , INDIA.**

Summary

Pharmacotherapy in the elderly is complicated by multifactorial issues, including age-related physiologic changes, the presence of multiple chronic disease states, functional changes in neuropsychiatric and physical abilities, and the patient's desire versus ability to comply with recommended therapy. Adverse drug reactions and interactions are more common than in the general population. The ageing process affects absorption, distribution, biotransformation, and excretion of drugs. These changes often influence the dosage regiments, dosage form, and route of administration. Biotransformation primarily occurs in the liver. As hepatic function declines, drugs may be metabolized more slowly, resulting in an altered first-pass effect of orally administered drugs. The geriatric dosing axiom, "start low and go slow" is based on pharmacokinetic considerations and concern for adverse drug reactions, not from clinical trial data. In the absence of generalizable dosage guidelines, individualization via effect titration is required.

Introduction.

“GERIATRICS” is a branch of medicine that focuses on health care of the ELDERLY.

Conventionally elderly population has been defined as individuals aged 65yrs and above.

Geriatrics AIMS to –

- promote health.
- Prevent and treat disorders and diseases among elderly.

Geriatrics differs from gerontology; Gerontology is the study of aging process as such.

“AGING” can be defined as progressive, universal decline in functional reserve in organism over time.

THEORIES OF AGING.

Aging is considered, by some as convergence of disease processes. However, various theories have been put forward to explain primary process of aging independent of disease.

a) FREE RADICAL THEORY.

- Proposed by Denman Harman in 1950.
- States that aging is a consequence of free radical damage by reactive oxygen species, like superoxide, hydroxyl radical, hydrogen peroxide and singlet oxygen.
- Primary site of production of free radicals is mitochondria, byproduct of oxidative metabolism.
- Other sources are phagocytic process, prostaglandin synthesis, cytochrome P450 enzyme and ionizing radiations.
- Oxidative injury minimized by enzymes superoxide dismutase, catalase, glutathione peroxidase, glutathione transferases and thiol specific antioxidant enzymes.

These enzymes along with low molecular weight substances ascorbate, glutathione, carotene, tocopherol and uric acid serve as free radical scavengers.

Reactive oxygen species cause deleterious changes to molecular DNA, lipids, proteins and prostaglandins.

Accumulation of these changes (in proteins specially) constitutes the basis of aging.

b) MITOCHONDRIAL THEORY OF AGING.

Reactive oxygen species generated in the mitochondria cause somatic mutation of mitochondrial DNA. Accumulation of such mutations leads to error in mitochondrial DNA encoded polypeptide, leading to defective electron transfer activity and oxidative phosphorylation, increased free radical formation and AGING.

c) TELOMERE AND CELLULAR SENESCENCE THEORY.

Telomeres are redundant DNA sequences, at the ends of chromosome, essential for mitoses.

With each cell division, telomeres shorten and cell division inhibited.

Number of divisions determine the maximum life span of the organism – HAYFLICK LIMIT.

Germ line cells contain telomerase enzyme, maintains the telomeric length.

Limitation: brain, contains non dividing cells but still ages.

d) APOPTOSIS.

Aging associated with up regulation of apoptosis.

Example : brain apoptosis seen in age related neurodegenerative diseases.

Cause: genetically regulated or oxidative stress is not yet clear.

e) GENETIC MECHANISM OF AGING:

Based on the observation that lifespan of given species is fixed and human aging has a hereditary component. A Scandinavian twin study, states that genes do influence longevity by influencing the underlying aging process and disease susceptibility.

Example: WERNER's SYNDROME.

Condition in which humans age at markedly accelerated rate.

Due to mutation in *wrn* gene that codes DNA helicases.

Helicases splits DNA strand before replication.

f) CALORIC RESTRICTION.

Refers to diet in which calories are limited by 30- 40%.

Decreases metabolism and decreased production of free radicals.

HISTORY.

“*THE CANON OF MEDICINE*” was the first book written on elderly care by Abu Ali Ibn Sina in 1025.

First modern geriatric hospital was found in Belgrade, Serbia in 1881 by doctor Laza Lazarevec.

The term “GERIATRICS” was proposed in 1909 by Dr. Ignatz Leo Nascher,Former chief of clinic in Mount Sinai Hospital (New York) and also Father of geriatrics.

British geriatrician Bernard Isaacs, described “giants of geriatrics”

- Immobility
- Instability
- Incontinence
- Impaired intellect

DEMOGRAPHY.

According to projections by UN population division, there will be two elderly persons for every child in world by 2050.

The number of people >65yrs are increasing constantly.

Currently <20% of total population are 60yrs and above, which is expected to rise to 32% by 2050.

The number of very elderly (>85) is considered the fastest growing group.

8.5% of the total Indian population is elderly.

SPECIAL DRUG CONSIDERATIONS IN ELDERLY.

Many morphological and functional changes are typical for aging organism.

They are---

- Biological age
- Polymorbidity
- Changed symptomatology of disease
- Changed course of disease
- Complications of disease
- Specific geriatric syndromes
- Predisposition to adaptation failure
- Changed reactivity to drugs
- Social dimension of disease in elderly

BIOLOGICAL AGE.

Progressive constriction of homeostatic reserve of organ system, homeostenosis.

Body composition:

- Decreased total body water.
- Decreased lean body mass.
- Decreased plasma albumin.
- Decreased bone mass.
- Increased body fat.
- Increased acid glycoprotein.

CNS: Cognitive deficits

Weight and size of brain decreased

CVS:

- Decreased cardiac output
- Decreased baroreceptor activity
- Decreased myocardial sensitivity to β -agonist/antagonist.

- Increased peripheral resistance.

GIT: Increased gastric pH.

Decreased GIT blood flow.

Delayed gastric emptying.

Liver: Decreased hepatic blood flow.

Renal: Decreased GFR

Decreased renal blood flow.

Decreased tubular secretion.

Endocrinol: Increased incidence of diabetes and thyroid disorder.

Genito urinary: Prostatic hypertrophy

Vaginal atrophy

Incontinence.

EFFECTS OF AGING ON DRUG ACTION. (Pharmacokinetics)

ABSORPTION.

- Drug formulation.
Tablets/capsules difficult to swallow.
Liquid dosage form preferred.
- Reduced gastric acid production
- Raises gastric pH
- May alter solubility of some drugs (ASA etc)
- Longer gastric emptying
- Delay or reduce absorption
- Decreased GI motility.
- Decreased intestinal blood flow.
- Reduced muscle mass –IM administration affected.
- Loss of subcutaneous fat
- Increased rate of absorption of topical medications
- Increased fragility of veins

IV administration more difficult

DISTRIBUTION –

- Age-associated changes in body composition can alter drug distribution
- Older people – have less body water and lean body mass, but greater fat stores
- Cardiac output is also decreased.
- Water soluble drugs have lower volume of distribution e.g. digoxin

- Fat soluble drugs – increased volume of distribution – longer to reach steady state and longer to be eliminated e.g. benzodiazepines
- Drugs bound to proteins-

higher proportion unbound and active in the elderly e.g. anticonvulsants (phenytoin). Unbound form of basic drugs (lidocaine, propanalol) decreases, as AAP increases.

METABOLISM-

- Most common site – liver
- Decreased liver size , mass and blood flow with aging.
- Reduced metabolic clearance of drugs due to decreased metabolizing enzymes.
- Hepatic metabolism occurs by two mechanisms-

Phase 1 reactions.

- Involves microsomal enzyme mixed function oxidase system.
- Isoenzymes: CYP3A4, CYP1A2, CYP2D6, CYP2C.
- Produces compounds which are pharmacologically active.
- This enzymatic reaction is slowed in elderly.

Phase 2 reactions

- Conjugation reactions.
- Produces inactive metabolites.
- Unaffected by aging.

ELIMINATION.

- Reduction in number of functioning nephrons
- Decreased glomerular filtration rate (50%)
- Longer half-life of medications
- Increased side effects
- Increased potential for toxicity.

To calculate appropriate dose for renally eliminated medication estimation of creatinine clearance required.

Given by Cockroft and Gault equation -

$$\text{CrCl (ml/min)} = (\text{LBW in kg})(140-\text{age in years}) \times (0.85 \text{ if female}) / (72)(\text{serum creatinine in mg/dl})$$

For men: LBW in kg = 50 + (2.3) (each inch > 5 feet).

For women: LBW in kg = 45 + (2.3) (each inch > 5 feet)

PHARMACODYNAMIC CHANGES.

- Changed sensitivity of target tissues
- Lowered sensitivity of receptors.
- Reduced number of receptors
- Increased penetration through blood brain barrier.
- Depletion of neurotransmitters.
- Impaired baroreceptor response to BP changes.
- Altered end organ sensitivity – exaggerated pharmacological response.

Example: increased susceptibility to bleeding complication of heparin in elderly.

Hence, dose adjustment of drugs become necessary as the net effect of drug becomes unpredictable.

MEDICATION RELATED PROBLEMS IN GERIATRICS.

- Polypharmacy.
- Adverse drug reactions.
- Compliance.
- Appropriateness of therapy.

POLYPHARMACY

- Multiple prescription and over the counter drugs.
- Individuals >65 are leading consumers of medications.
- Account for 34% of prescription medication and 50% OTC medication.
- >80% take one medication daily.
- Community dwelling individuals take on an average 4 medicines.
- Nursing home residents on an average take 9 medications daily.

ADVERSE DRUG REACTIONS.

Common in older people compared to young.

May have atypical presentation.

Example: digoxin toxicity.

Older patients complain of anorexia and weight loss instead of nausea and vomiting.

REASONS :

- Multiple chronic diseases requiring treatment with multiple potent medications.
- Several physicians prescribing therapy independently.
- Inappropriate self medication.
- Patient's noncompliance.
- Inadequate patient education.
- Inappropriate identification of altered presentation of adverse drug reaction.
- Age related physiological changes.

COMPLIANCE.

Extent to which patient's behavior coincides with prescriber's planned medical regimen.

Non compliance occurs in half to one-third of elderly patients.

RISK FACTORS:

- Long term therapy/chronic diseases.
- Multiple medications.
- Multiple dosing schemes.
- Psychiatric illness.
- Cognitive impairment.
- Ineffective communication with health care professionals

APPROPRIATENESS OF THERAPY.

Strategies have been developed to foster appropriate medication to the geriatric patient.

Sedative-hypnotics, Anti anxiety drugs.

Drugs to be AVOIDED:

- Barbiturates.
- Diazepam.
- Flurazepam.
- Chlordiazepoxide, Clorazepate.

REASON :

- Prolongation of half-life.
- ataxia
- loss of postural reflex.

PREFERRED : Oxazepam, lorazepam , alprazolam, temazepam.

ANALGESICS

OPIOIDS.

Should be avoided.

REASON : respiratory depressant effect.

PREFERRED : Codeine, meperidine, morphine, buprenorphine.

NSAIDS.

Should be avoided.

REASON :

- GI bleeding.
- Renal damage.
- CNS side effects. (indomethacin)
- Hematological toxicity. (phenylbutazone)

PREFERRED: Ibuprofen, nimesulide, COX-2 inhibitors.

Corticosteroids can be used, along with calcium and Vitamin-D and with histamine antagonists.

ANTIPSYCHOTICS.

AVOIDED: Phenothiazines, haloperidol

REASON :

- Extra pyramidal side effects.
- Anticholinergic side effects.
- postural hypotension.

PREFERRED: Thioridazine, olanzepine, aripiprazole pimozide(QT interval should be watched)

ANTIDEPRESSANTS.

AVOIDED: TCA (except nortriptyline, desipramine)

TCA and antipsychotic combination

REASON : postural hypotension.

anticholinergic side effects.

PREFERRED: SSRIs.

ANTI MANIA

AVOIDED: Lithium.

REASON : Renal toxicity.

PREFERRED: Carbamazepine, valproic acid.

GENERAL ANAESTHETICS.

AVOIDED: Halothane, Enflurane, Thiopental and Pancuronium.

REASON : Hepatotoxicity (halothane)

Epilepsy (Enflurane)

PREFERRED: Isoflurane (expensive)

midazolam/ propofol – for minor surgeries.

thiopental and pancuronium in low doses.

ALZHEIMER'S DISEASE.

Preferred: Donepezil, rivastigmine, galantamine.

Avoided: Tacrine.

Reason : Hepatotoxicity, CNS toxicity.

CARDIOVASCULAR DRUGS.

Antihypertensive drugs.

Avoided: propanalol, methyl dopa, thiazide diuretics (high doses).

Reason: hypokalemia, hyperglycemia, hyperuricaemia precipitates arrhythmias, gout, type 2 DM.

Methyl dopa : deep sedation, postural hypotension.

propanalol : not safe in elderly with asthma, PVD, CHD.

Preferred:

- thiazide (minimum effective dose) with potassium sparing diuretics.
- selective beta blocker/ACEI/ARB/CCB.

CARDIAC GLYCOSIDES.

Should be avoided.

Reason:

- Increased sensitivity to arrhythmogenic action of digoxin.
- hypokalemia, hypoxemia, hypomagnesaemia precipitates
- Toxicity.
- Clearance decreased, half life prolonged.

Safe alternative: loading and maintenance dose should be reduced.

ANTIARRHYTHMICS.

Avoided: Disopyramide, quinidine, xylocaine.

Reason : clearance decreased, half life prolonged, antimuscarinic effects, negative ionotropic cardiac effects (quinidine)

Safe alternative: dose reduction of xylocaine.

PLATELET INHIBITORS.

Avoided: Dipyridamole.

Reason : Postural hypotension, coronary steal phenomenon.

Preferred: clopidogrel, aspirin.

ANTI ANGINAL DRUGS.

Avoided: Isosorbide dinitrate, verapamil.

Reason : tachycardia, hypotensive action. (Isosorbide dinitrate) conduction abnormalities. (verapamil)

Preferred: Diltiazem.

DRUGS FOR RESPIRATORY SYSTEM.

Avoided: Ephedrine, isoproterenol, theophylline.

Reason : rise in BP, tachycardia, urinary hesitancy (ephedrine) tremor, tachycardia, arrhythmias. (isoprenaline) tremors, CNS stimulation, diuresis, arrhythmias- theophylline

Preferred: salbutamol, terbutaline, budesonide, terbutaline.

ANTIBIOTICS.

Avoided : penicillin, cephalosporin, fluoroquinolones, nitrofurantoin.

Reason : prolonged half life.
pulmonary reaction and peripheral neuritis. (nitrofurantoin)

Preferred : ceftriaxone, cefoperazone.
tobramycin may be used.
dose adjustment may be done.

ANTIDIABETIC DRUGS.

Avoided : Chlorpropamide, Glibenclamide.

Reasons :

- Half life increased
- serious hypoglycemic episodes.

Preferred : Glipizide, Glicazide or metformin + metformin.

GASTROINTESTINAL DRUGS.

ANTIEMETICS

Avoided : antihistaminics, metoclopramide.

Reason : anticholinergic side effects. (anti histaminic)

extra pyramidal symptoms. (metoclopramide)

Preferred : domperidone , ondansetron.

LAXATIVES – PURGATIVES.

Avoided: Castor oil, Magnesium Sulphate, liquid paraffin and phenolphthalein.

Reason: pelvic congestion, intestinal mucosa damage. (castor oil)

hypomagnesaemia(Magnesium Sulphate)

Cardio toxicity (phenolphthalein)

foreign body granuloma (liquid paraffin)

Preferred: milk of magnesia, enema, senna preparation.

GERIATRIC DRUG THERAPY : TREATMENT GOALS.

- Resolve symptoms of specific condition and slow progression of negative outcome of the condition.
- Avoid medication related problems.
- Use least number of medications possible.
- Initiate therapy with a low dose and increase slowly.
- Set an appropriate duration of therapy and consider dosage reduction.
- Based on patient's clinical status and co-morbid conditions appropriate pharmacological alternative should be selected.
- Minimize the number and dose of medication with effects on CNS.
- Avoid "inappropriate medications"- Beer's criteria.
- Watch out for potential drug-drug and drug-disease interactions.
- Expensive medications should be avoided.
- Ask patient to bring in all medications.(OTC, herbal preparations.)
- Ask patient how each medication is being taken.

- Look for medications with duplicate therapeutics and pharmacological profiles.
- Make sure patient and care giver what medication is for, how and when to take it and possible side- effects.

Always review any changes in writing with the patient and caregiver, provide the changes in writing.

PREVENTIVE CARE:

Mortality and morbidity from pneumococcal pneumonia, influenza, and tetanus infection are very high in the geriatric population.

Older patients show a response to the antibody formation from the polyvalent pneumococcal vaccine.

All persons 65 years and above should receive the pneumococcal vaccine.

A favorable antibody response is likewise elicited from annual influenza vaccine.

CONCLUSION:

When providing care for the geriatric patients, it is necessary to evaluate the need for existing or new medications.

In summary, a regular review of patients drug therapy should be done to screen for the following:

- Is each medication necessary?
- Are non pharmacological alternatives available?
- Is the lowest effective dose being used?
- Are there any unaddressed medical or drug related problems?

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