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Pharmacokinetic, Pharmacodynamic Changes In Geriatrics And Beers Criteria: An Overview

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ABSTRACT

The controlled processes that provide functional integration between cells and organs are impaired in the elderly persons. As a result, there occur failures to maintain homeostasis under physiological stress conditions. In the advancing age, the important pharmacokinetic as well as pharmacodynamics properties are tremendously changed. In elderly patients failure to maintain the pharmacokinetic changes include decreased absorption of number of drugs, increase in volume of distribution of drugs, decrease hepatic and renal clearances where as pharmacodynamic changes involve usually altered sensivity to number of classes of drugs such as cardiovascular, anticoagulants and psychotropic drugs. The inappropriate medication use is a major health care issue for the elderly population. Beers criteria were developed in 1991 to define inappropriate medication use of elderly. By developing these new criteria, a clear picture emerged for a list of medications with questionable benefit and/or significant risk that should be avoided in older adults.

Keywords: Geriatrics, Pharmacokinetic, Pharmacodynamic Factors, Beers Criteria.

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INTRODUCTION

There has been a steady increase in the number of elderly people, defined as those over 65 year's age, since the beginning of the 20th century. India is in a phase of demographic change. As per the 1951 census, the population of the elderly in India was 20 million, in1991 it was 57 million. The number of elderly persons in between 1991 and 2001 increasing enormously and it has been expecting that by the year 2050, the number of elderly people would increase to about 324 million.[1] The significant increase in the number of elderly people will have important social, financial, and health care planning implications.

The elderly people often have multiple and chronic disease. Therefore, it is not surprising that they are the major consumers of drugs. Elderly people receive about one third national health services (NHS) prescriptions in the U.K. In most developed countries about 25-40% of the expenditure of the elderly people is spent on drug usage.

A survey of drug usage in elderly people showed that 70% had been on prescribed medication and 40% had taken one or more prescribed drugs (Polypharmacy) within the previous 24 hours. 32% were taking cardiovascular drugs, and other therapeutic categories used in decreasing order of its frequency are for: disorder of the central nervous system (24%), musculoskeletal system (10%), gastrointestinal system (8%) and respiratory system (7%). The most commonly used drugs were: diuretics, analgesics, hypnotics, sedatives, anxiolytics, antirhematic drugs and β-blockers.

Institutionalized patients tend to be on larger numbers of drugs compared with patient in the community. One study has shown that patients in long-term care facilitates are likely to be receiving on an average eight drugs. Psychotropic drugs are used widely in nursing or residential homes.

For optimal therapy in the elderly, knowledge of age-related physiological and pathological changes that might affect handling of and response to drugs is essential. The age related pharmacokinetic and pharmacodynamics changes which might affect drug therapy and the general principles of drug use in the elderly.

Pharmacokinetic changes:

Ageing consequences in many physiological changes that could theoretically affect absorption first pass metabolism, protein binding, distribution and elimination of drugs. Age related changes in the gastrointestinal tract, liver and kidney are:

Absorption:

There is a delay in gastric emptying, reduction in gastric acid output and splanchnic blood flow with ageing. [2, 3] These changes do not significantly affect the absorption of the majority of drugs. Although the absorption of some drugs such as digoxin may be slower, the overall absorption is similar to that in the young.[4]

In elderly persons, causes of impaired drug absorption include altered gastric empting, decreased intestinal surface area and GI blood flow,[4] higher incidents of achlorhydria, bacterial overgrowth in small intestine, reduced liver size, reduced golmerular filtration and reduced renal tubular filtration.[2] Active transport mechanisms are decreased. [5][6]

First-pass metabolism and bioavailability:

After absorption, drugs are transported via the portal circulation to the liver, where lipid-soluble agents are metabolized extensively (more than 90-95%). These results in a marked reduction in systemic bioavailability, obviously, even minor reductions in first-pass metabolism can result in a significant increase in the bioavailability of such drugs.[7]

Impaired first-pass metabolism has been demonstrated in the elderly for several drugs, including clomethiazole, labetolol, nifidifine, nitrates, propanolol and verapamil. The clinical effects of some of these, such as the hypotensive effect of nifidifine, may be significantly enhanced in the elderly. [8,9,10]

Distribution:

The age related physiological changes which may affect drug distribution are:

- Reduced lean body mass
- Reduced total body water
- Increased total body fat
- Lower serum albumin level
- α_1-Acid glycoprotein level unchanged or slightly raised.

Increased body fat in the elderly results in an increased volume of distribution for fat-soluble compounds such as clomethiazole, diazepam, desmethyl-diazepam and thiopental. On the other hand reduction in body water results in decrease in the distribution volume or water soluble drugs such as cimetidine, digoxin and ethanol.[11, 12]

In old age, the albumin content is lowered and free concentration of drugs that bind primarily to it is increased. [13] Old age is also characterized by an increase in the levels of AAG (α_1-Acid Glycoprotein) and thus decreased free concentration is observed for drugs that bind to it. The situation is complex and difficult to generalized for drugs that bind to both HSA (Human Serum Albumin) and AAG (α_1-Acid Glycoprotein), e.g. lidocaine and propanolol.[13]

Protein binding:

Acidic drugs tend to bind plasma albumin, while basic drugs bind to α_1-acid glycoprotein. Plasma albumin level decrease with age and therefore the free fraction of acidic drugs such as cimetidine, furosemide and warfarin will increase. Plasma α_1-acid glycoprotein levels may remain unchanged or may rise slightly with ageing, and thus may result in minimal reduction in free fractions of basic drugs such as lidocaine (lignocaine). Disease-related changes in the level of this glycoprotein are probably more important than age per se. [13, 14]

The age-related changes in distribution and protein binding are probably of significant only in the acute administration of drugs because, at steady state, the plasma concentration of a drug is determined primarily by free drug clearance by the liver and kidneys rather than by distribution volume or protein binding.[13]

Renal clearance:

Although there is a considerable interindividual variability in renal function in the elderly, in general the golmerular filtration rate (GFR), effective renal plasma flow and renal tubular function declines. [15] Because of the marked variability in renal function in the elderly, the dosage of predominantly renally excreted drugs should be individualized. Reduction in dosages of drugs with a low therapeutic index, such as digoxin and aminoglycosides, may be necessary. Dosage adjustments may not be necessary for drugs with a wide therapeutic index, for example penicillins.[16,17]

Hepatic clearance:

Hepatic clearance of a drug is dependent on hepatic blood flow and the steady state excretion rate. Hepatic excretion is dependent upon liver size, liver blood flow, uptake into hepatocytes, and the affinity and activity of hepatic enzymes and mainly affects the clearance of drugs with a high extraction ratio. Liver size falls with ageing and there is a decrease in hepatic mass of between 20% and 40% between the third and tenth decade. Hepatic blood flow falls equally with decline liver size, although it is recognized that the microsomal monooxygenase enzyme systems are significantly reduced in ageing.[18]

Impaired clearances of many hepatically eliminated drugs have been demonstrated in the elderly and have shown significant decrease in the clearance of several drugs metabolized by asynthetic (phase-1or functionalisation) pathways in the liver. Morphologically changes rather than impaired enzymatic activity appears to be the main cause of impaired elimination of these drugs. In frail debilitated elderly patients, however, the activities of drug-metabolizing enzymes such as plasma esterase's and hepatic glucuronyltranferases may well be impaired.[19]

PHARMACODYNAMIC CHANGES:

Molecular and cellular changes that occur with ageing may delay the response of drug in the elderly. There is, however, limited information about these alterations because of the technical difficulties and ethical problems involved in measuring them. It is not surprising therefore that there is relatively little information about the effect of age on pharmacodynamics.

Changes in pharmacodynamics in the elderly may be considered under two headings.

- Those due to a reduction in homeostatic reserve
- Those that is secondary to changes in specific receptor and target sites.

Reduced homeostatic reserve:

Orthostatic circulation responses:

In normal elderly subjects there is blunting of the reflex tachycardia that occurs in young subjects on standing or in response to vasodilatation. Structural changes in the vascular tree that occur with ageing are believed to contribute to this observation, although the exact mechanism is unclear. Antihypertensive drugs, drugs with α receptor blocking effects (e.g. tricyclic anti depressants, phenothiazines and some butyrophenones), drugs which decrease sympathetic outflow from the central nervous system (e.g. barbiturates, benzodiazepines, antihistamines and morphine) and antiparkinsonian drugs (e.g. levodopa and bromocripine) are therefore more likely to produce hypotension in the elderly.[20, 21]

Postural control:

Postural stability is normally achieved by static reflexes, which involve sustained contraction of the musculature, and phasic reflexes, which are dynamic, short-term and involve transient corrective movements. With ageing, the frequency and amplitude of corrective movements increase and an age-related reduction in dopamine (D_2) receptors in the striatum has been suggested as the probable cause. Drugs which increase postural sway, for example hypnotics and tranquilizers, have been shown to be associated with the occurrence of falls in the elderly.[22,23]

Thermoregulation:

There is an increased prevalence of impaired thermoregulatory mechanisms in the elderly, although it is not universal. Accidental hypothermia can occur in the elderly with drugs that produce sedation, impaired subjective awareness of temperature, decreased mobility and muscular activity, and vasodilatation. Commonly implicated drugs include phenothiazines, benzodiazepines, tricyclic antidepressants, opioids and alcohol, either on its own or with other drugs.

Cognitive function:

Ageing is associated with marked structural and neurochemical changes in the central nervous system. Cholinergic transmission is linked with normal cognitive function, and in the elderly the activity of choline acetyltransferases, a marker enzyme for acetylcholine, is reduced in some areas of the cortex and limbic system. Several drugs cause confusion in the elderly. Anticholinergics, hypnotics, H_2 antagonists and β- blockers are common examples.[24]

Visceral muscle function:

Constipation is a common problem in the elderly as there is a decline in gastrointestinal motility with ageing. Anticholinergic drugs, opiates, tricyclic antidepressants and antihistamines are more likely to cause constipation or ileus in the elderly. Anticholinergic drugs may cause urinary retention in elderly men, especially those who have prostatic hypertrophy. Bladder instability is common in the elderly and urethral dysfunction more prevalent in elderly women. Loop diuretics may cause incontinence is such patients.[25, 26]

Age related changes in specific receptor and target sites:

Many drugs exert their effect via specific receptors. Response to such drugs may be altered by the number (density) of receptors, the affinity of the receptor, post receptor events within cells resulting in impaired enzyme activation and signal amplication, or altered response of the target tissue itself. Ageing is associated with some of these changes.

α- adrenoreceptor:

α_2 adrenoreceptor responsive to be reduced with ageing while α_1 adrenoreceptor responsiveness appears to be unaffected.

β- adrenoreceptor:

β-adrenoreceptor function declines with age, it is recognized that the chronotropic response to isoprenaline infusion in the elderly produces less β-adrenoreceptor blocking effect than in the young. In isolated lymphocytes, studies of cyclic adenosine monophosphate (cAMP) production have shown that on β-adrenoreceptor stimulation the dose-response curve is shifted to the right, and the maximal response is blunted.[27]

An age-related reduction in β-adrenoreceptor density has been shown in animal adipocytes, erythrocytes and brain, and also in human lymphocytes in one study, although this has not been confirmed by other investigators. As maximal response occurs on stimulation of only 0.2% of β-adrenoreceptor, a reduction in the number by itself is unlikely to account for age-related changes. Some studies have shown a reduction in high-affinity binding sites with ageing, in the absence of change in total receptor numbers, and other have suggested that there may be impairment of post receptor transduction mechanisms with ageing that may account for reduced β-adrenoreceptor

function.[28, 29]

Cholinergic system:

The effect of ageing on cholinergic mechanisms is less known. Atropine produces less tachycardia in elderly humans than in the young. The clinical significance of this observation is unclear.[27]

Psychotropic drugs:

The elderly are more sensitive to benzodiazepines than the young, and the mechanisms of this increased sensitivity is not known. Habituation to benzodiazepines occurs to the same extent in the elderly as in the young.[30, 31]

Anticoagulant:

The elderly are more sensitive to warfarin. This phenomenon may be due to age-related changes in pharmacodynamics factors. The exact mechanism is unknown.[32,33]

Digoxin:

Digoxin mainly eliminated through kidneys and digoxin clearance is directly proportional to creatinine clearance (CrCl). Systemic clearance is decreased with age. The elderly appear to be more sensitive to the adverse effects of digoxin, but not to the cardiac effects.[34]

BEERS CRITERIA:

Inappropriate medication use is a major health care issue for the elderly population. Older patients are more at risk for adverse medication outcomes because they often have complex drug regimens and age related changes in drug pharmacokinetics and pharmacodynamics.[35] Potentially inappropriate prescriptions (PIPs), defined as prescriptions in which risks outweigh benefits, have been assessed in various settings using lists of explicit criteria most often based on that developed by Beers. PIPs have been estimated to affect 4.8% to 45.6% of the elderly population. [35,36]

Beers criteria, the potentially inappropriate use of medications in elderly patients is the principle for healthcare professionals to improve the safety of prescribing medications for older adults which may prevent harmful side effects, including those that could be life-threatening and other "adverse drug events" (ADE's). These criteria's are used to monitor and improve the quality of healthcare in geriatrics clinical care, training, research, and healthcare policy to develop performance measures and document outcomes. As more people reaches geriatric status, the delivery of safe and effective healthcare in this special population has become increasingly important.[37]

The original Beers criteria were developed (late Mark H. Beers, MD) in 1991 to define inappropriate medication use in a nursing home population. Since its origin; these criteria's have been revised and updated to define potentially inappropriate use of medications in elderly people. These criteria's have been widely used over the past decades for studying prescribing patterns within populations; educating clinicians; and evaluating health outcomes, cost, and utilization data.

The *2012 AGS Beers Criteria* identify and group medications into three different categories instead of just two, as it was done previously for the elderly people. They are medications to avoid in older adults regardless of diseases or conditions; medications considered potentially inappropriate when used in older adults with certain diseases or syndromes; and a new, third group of medications that should be used with caution in older adults. This overview will present only some of the medications mentioned in the 2012 Beers criteria. Medications to avoid the revised Beers criteria list 34 potentially inappropriate medications and classes to avoid in older adults. New additions to the criteria include megestrol, glyburide, and sliding-scale insulin. Specific recommendations and rationales are summarized in Table 1.[38,39]

Use with caution:

A new addition to the Beers criteria is a list of agents that should be used with caution in this patient population. Specific recommendations and rationales are summarized in Table 2

Table 2: Potentially inappropriate medications to be used with caution in older adults.

Drug or drug class	Recommendation	Rationale
Aspirin for primary prevention of cardiac events	Use with caution in patients ≥ 80 years of age	Lack of benefit vs. risk in patients ≥ 80 years of age
Antipsychotics, carbamazepine, mirtazapine, SNRIs, SSRIs, TCAs, carboplatin, cisplatin, vincristine)	Use with caution	May exacerbate syndrome of inappropriate antidiuretic hormone secretion or hyponatremia
Prasugrel (Effient—Daiichi Sankyo, Eli Lilly)	Use with caution in patients ≥ 75 years of age	Greater risk of bleeding in older adults
Dabigatran (Pradaxa—Boehringer Ingelheim)	Use with caution in patients ≥ 75 years of age or in those with CrCl < 30 mL/min	Greater risk of bleeding in older adults; lack of evidence for efficacy and safety in those with CrCl < 30 mL/min
Vasodilators	Use with caution	May exacerbate episodes of syncope in those with a history of syncope

Abbreviations used: CrCl: Creatinine Clearance; SNRI: Serotonin–Norepinephrine Reuptake Inhibitor; SSRI: Selective Serotonin Reuptake Inhibitor; TCA: Tricyclic Antidepressant.

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Table1: Examples of medications to avoid in older adults regardless of diseases or conditions.

Drug or Drug class	Rationale
Alpha-1 blockers	May cause orthostatic hypotension; do not use as an antihypertensive
Alpha agonists (e.g., clonidine, guanabenz, methyldopa)	High risk for CNS adverse events
Class Ia, Ic, and III antiarrhythmics	Evidence suggest that rate control yields more benefits than rhythm control in older adults; specific agents associated with numerous toxicities
Digoxin > 0.125 mg/d	Higher doses do not result in additional benefit and risk of toxicity high especially in those with a reduced renal function
Immediate-release nifedipine	Hypotension and potential risk of precipitating MI
Antipsychotics, both first and second generation	Increased risk of stroke and mortality in those with dementia
Tertiary TCAs Highly anticholinergic	Highly anticholinergic
Barbiturates	High rate of physical dependence; overdose a concern
Benzodiazepines	Older adults more sensitive to effects; increases risk of cognitive impairment, delirium, falls, and fractures
Non benzodiazepine hypnotics (e.g., zolpidem)	Adverse events similar to those observed with benzodiazepines
Sliding scale insulin	Higher risk of hypoglycemia without improving hyperglycemia
Megestrol	Minimal effect on weight with accompanying adverse events
Long-acting sulfonylurea's (i.e., chlorpropamide, glyburide)	Greater risk of prolonged hypoglycemia
Metoclopramide	Associated with extra pyramidal adverse events
First-generation antihistamines	Highly anticholinergic; greater risk of confusion, dry mouth, and other anticholinergic adverse events
Antispasmodics	Highly anticholinergic; questionable effectiveness
Short-acting, oral dipyridamole	May cause orthostatic hypotension
Ticlopidine	Safer alternatives available
Nitrofurantoin	Pulmonary toxicity may occur; lack of efficacy data in those with a CrCl < 60 mL/min
Estrogens	Evidence of carcinogenic potential and lack of cardiovascular or cognitive benefits
Meperidine	Not effective for pain control and associated with neurotoxic effects
Non-COX selective oral NSAIDs	Increased risk of GI bleed and peptic ulcer disease in high-risk groups
Pentazocine	CNS adverse events
Skeletal muscle relaxants	Poorly tolerated because of anticholinergic effects

Abbreviations used: CrCl: Creatinine Clearance; CNS: central nervous system; COX, cyclooxygenase; GI: gastrointestinal; NSAID: Non Steroidal Anti-Inflammatory Drug; TCA: Tricyclic Antidepressant.

CONCLUSION:

The number of elderly patients, especially those aged over 65 years, is progressively increasing, and they are accounting for an ever-increasing proportion of health care expenditure. Understanding age-related changes in pharmacodynamic factors, avoiding Polypharmacy and regular and critical review of all drug treatment will help in the rationalization of drug prescribing, reduction in drug-related morbidity and also the cost of drug therapy for this important subgroup of patients. The inappropriate prescribing is highly prevalent in the elderly long-term care population. The use of an explicit criteria list to identify potentially inappropriate prescriptions (PIPs) (by using Beers Criteria) is a first step towards identifying most critical issues and implementing strategies to improve quality of care and safety of elderly people.

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