AN OVERVIEW OF GERIATRIC PHARMACOLOGY

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Received: 6 September 2012, Revised and Accepted: 16 October 2012

ABSTRACT

Elderly patients frequently experience multiple illnesses and take many drugs concurrently. The combination of altered drug activity, impaired homeostasis, and the use of multiple drugs by elderly patients results in frequent adverse drug reactions. Although they can be difficult to recognize in elderly patients, adverse drug reactions are a frequent cause of morbidity and may necessitate hospitalization. Because the risk of adverse drug reactions increases with the number of drugs taken, it is important to discontinue any treatment that is not efficacious. Because of neurological, visual and auditory disabilities, elderly patients may have difficulty complying with complicated drug regimens. Some chronic diseases in elderly patients cannot be effectively treated with drugs. The survey studies regarding utilization of medicine as well as the education in elderly patients may reduce the morbidity in general. Furthermore, the education and the training of doctors for prescribing drugs in elderly patients in view of altered drug behavior in these patients in view of changed pharmacokinetic and pharmacodynamic behavior of the drugs will be remedial measures to decrease the morbidity of elderly patients to a greater extent.

Keywords:

INTRODUCTION

Society has traditionally classified everyone over 65yrs as elderly. ‘Geriatrics’ apply to persons over 75yrs. Elderly persons are our most medicated group of patients and are prescribed the highest proportion of medications. Pharmacotherapy is single most important intervention for care of the majority of elderly patients. This group today represents approximately 13% of total population but purchase 33% of all prescription drugs, furthermore, by 2040, it is estimated that they will represent 25% of total population and will buy 50% of all prescription drugs. The number and proportion of elderly people in the population are increasing as a result of decreasing birth rates and improved medical and economic factors that favor a longer life expectancy. The dose of the drug in elderly patient is to be administered cautiously. In the early days, decisions about drug selection and the dosage in the elderly were largely based on trial and error. Sound information on drug disposition and tissue and cellular responses to drugs in the elderly has been obtained only recently.

Adverse drug reactions are an important cause of morbidity and hospital admission in elderly patients. 85 to 95% of ambulatory elderly take at least 1 medication, with an average of 3-4 per day. In a large, multicentre trial, adverse reactions were a contributing cause in 10.5% of consecutive geriatric admissions. The enhanced adverse drug reaction may be due to impaired organ function, aging itself, altered drug kinetics and organ response and homeostatic counter-regulation to drug effect. The physiological changes that occur in elderly are shown in Table-1.

Table 1: Physiological Changes in Elderly.

<table>
<thead>
<tr>
<th>BODY COMPOSITION</th>
<th>↓ in total body water, ↑ in lean body mass, ↑ in fat, ↓ in plasma albumin, ↑ in α1 acid glycoprotein</th>
</tr>
</thead>
<tbody>
<tr>
<td>CNS</td>
<td>↓ in weight and size of brain, cognitive deficit</td>
</tr>
<tr>
<td>PULMONARY SYSTEM</td>
<td>↓ in total vital capacity, ↓ in maximum breathing capacity, ↓ in total alveolar surface, ↓ respiratory muscle strength</td>
</tr>
<tr>
<td>GVS</td>
<td>↓ in baroreceptor activity, ↓ in cardiac output, ↑ in total peripheral resistance</td>
</tr>
<tr>
<td>GASTROINTESTINAL SYSTEM</td>
<td>↑ in gastric pH, ↓ in GIT blood flow, Delayed gastric emptying</td>
</tr>
<tr>
<td>LIVER</td>
<td>↓ in hepatic blood flow</td>
</tr>
<tr>
<td>RENAL</td>
<td>↓ in GFR, ↓ in renal blood flow, ↓ in tubular secretion</td>
</tr>
<tr>
<td>GENITOURINARY SYSTEM</td>
<td>Prostatic hypertrophy (Males), Vaginal atrophy and menopause (females), Incontinence</td>
</tr>
<tr>
<td>ENDOCRINE</td>
<td>↑ in incidence of diabetes and thyroid disorder</td>
</tr>
<tr>
<td>IMMUNE SYSTEM</td>
<td>↓ in cell mediated immunity</td>
</tr>
</tbody>
</table>

PHARMACOKINETIC FACTORS

Drug absorption and bioavailability

Bioavailability of a drug depends on gastrointestinal absorption and the first pass metabolism in gastric mucosa and the liver. The process of aging brings about changes in gastrointestinal function such as increase in gastric pH, delayed gastric emptying, decreased motility, and decreased intestinal blood flow. The absorption of substances that are actively transported from the intestinal lumen including some sugars, minerals and vitamins may therefore be decreased in elderly patients. Apart from the pathological or surgical alterations in gastrointestinal function such as gastrectomy, pyloric stenosis, pancreatitis, regional enteritis, and malabsorption syndromes and concurrent administration of other drugs like cholestyramine and antacids may cause changes in drug absorption. Cholestyramine binds and decreases the absorption of many drugs including thiazides, anticoagulants, thyroxine, aspirin, PCM,
Penicillin while antacids decrease the absorption of drugs such as chlorpromazine, tetracycline, isoniazid. Plasma protein concentrations may also be altered in elderly patients. Plasma albumin concentrations are less causing increase in free concentration of acidic drugs such as naproxen, phenytoin and warfarin. In contrast, the concentration of α1-acid glycoprotein may be increased in the presence of chronic diseases that frequently occur in the elderly population, potentially increasing the binding of drugs such as antidepressants, antipsychotic drugs and β-blockers which are mainly bound to this protein. Plasma creatinine, on the other hand, is less likely to overestimate the creatinine mass to low concentrations, the adaptive response in proportion to body weight and lean body mass decreases, whereas, body fat as a percentage of body weight increases with aging. The increased body fat is associated with the increase in volume of distribution of fat-soluble drugs such as the benzodiazepines which leads to a more prolonged drug effect. Thus, it was demonstrated that the elimination half-life of diazepam was prolonged with age despite the fact that systemic clearance was unaffected. Change in organ blood flow with aging may also affect the rate of drug distribution. Some cross-sectional studies indicate that cardiac output decreases and peripheral vascular resistance increases with age. Hepatic and renal blood flow is decreased. Hepatic metabolism

Drug metabolism is determined by body composition, plasma protein binding, and organ blood flow. Total body water and lean body mass decreases, whereas, body fat as a percentage of body weight increases with aging. The increased body fat is associated with the increase in volume of distribution of fat-soluble drugs such as the benzodiazepines which leads to a more prolonged drug effect. Thus, it was demonstrated that the elimination half-life of diazepam was prolonged with age despite the fact that systemic clearance was unaltered. Change in organ blood flow with aging may also affect the rate of drug distribution. Some cross-sectional studies indicate that cardiac output decreases and peripheral vascular resistance increases with age. Hepatic and renal blood flow is decreased.

Hepatic Metabolism

Hepatic blood flow and liver mass change in proportion to body weight and decrease with aging. The rate of metabolism of many drugs by the cytochrome P450 enzyme system is decreased by 20% to 40% with aging. Examples include theophylline, propranolol, nortriptyline, alfentanil, fentanyl, alprazolam, triazolam, diltiazem, verapamil, and levodopa. Many benzodiazepines are metabolized by microsomal enzyme to active metabolites which are also eliminated by hepatic metabolism. Non-microsomal enzyme pathways may be less affected by age. Example-Ethanol metabolism by alcohol dehydrogenase and isoniazid elimination by acetylation are unchanged in elderly patients. Concurrent drug administration, illness, genetics and environmental factors including smoking may have more important effects on hepatic drug metabolism than age.

Renal Excretion

Renal blood flow, glomerular filtration rate and tubular function all decline with aging. In addition to physiological decline in renal function, the elderly patient is particularly liable to renal impairment due to dehydration, congestive heart failure, hypotension and urinary retention, or to intrinsic renal involvement e.g. diabetic nephropathy or pyelonephritis.

As lean body mass decrease with aging, the serum creatinine level is a poor indicator of (and tends to overestimate) the creatinine clearance in older adults. The Cockcroft-Gault formula should be used to estimate creatinine clearance in older adults:

\[
\text{Creatinine clearance} = \frac{(140 - \text{age} \times \text{weight (kg)})}{72 \times \text{serum creatinine in mg/dl}}
\]

(For women multiplied by 0.85)

Pharmacokinetic parameters are shown in Table II.

**Table 2: Physiological changes and pathological conditions affecting pharmacokinetic variables in elderly**

<table>
<thead>
<tr>
<th>Pharmacokinetic variable affected</th>
<th>Age-related physiological changes</th>
<th>Pathological Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DISTRIBUTION</strong></td>
<td>[C.O., total body water, *serum albumin conc, *α1 acid glycoprotein conc, *proportion of body fat]</td>
<td>Congestive heart failure, dehydration, oedema or ascitis, hepatic failure, malnutrition, renal failure</td>
</tr>
<tr>
<td><strong>METABOLISM</strong></td>
<td>[Hepatic mass, *hepatic blood flow]</td>
<td>CHF, fever, hepatic insufficiency, malignancy, malnutrition, thyroid disease, viral infection</td>
</tr>
<tr>
<td><strong>EXCRETION</strong></td>
<td>[Renal blood flow, *GFR, *tubular secretion]</td>
<td>Hypovolemia, renal failure</td>
</tr>
</tbody>
</table>

**PHARMACODYNAMIC CHANGES**

In addition to pharmacokinetic changes, organ response and homeostatic counter-regulation may be altered with aging. The physiological response includes both the direct drug effect and the homeostatic responses to that pharmacological effect. Decreased homeostatic counter-regulation with aging may be a significant cause of adverse drug reactions.

**Receptor Sensitivity**

β-adrenoceptor function in elderly patients has been more extensively studied than other receptor responses. It appears that the β-adrenoceptor agonist affinity is decreased with aging, perhaps secondary to elevated plasma catecholamine concentrations.

Elderly patients are known to be more sensitive to psychotherapeutic drugs. Impairment of psychomotor function by benzodiazepines, for example, occurs at lower concentrations in elderly than in young patients. Elderly patients appear to be more sensitive to the effects of morphine, warfarin, diltiazem, verapamil, enalapril, and levodopa.

**Impaired Homeostasis**

Homeostatic regulation requires appropriate sensing of an altered physiological state (whether due to disease or therapeutic intervention), endocrine or neurological transmission of sensory and regulatory signals, and appropriate organ compensatory responses. Impaired homeostasis is a frequent cause of adverse drug reactions as well as increased sensitivity to drug effects. For example, older individuals have an impaired ability to excrete free water load. Addition of hydrochlorothiazide further impairs free water excretion in elderly patients, placing the patient at risk of dilutional hyponatremia.

Most of the elderly patients are susceptible to congestive heart failure from the rapid infusion of saline. Cardiac output, renal function and endocrine response to volume overload are all decreased with age.

Volume depletion is also a risk. While the senescent kidney is able to decrease urinary sodium to low concentrations, the adaptive response is delayed and extracellular fluid loss may be significant during this period. Volume depletion is further exacerbated by diminished plasma rennin activity, the basal level of which is decreased by 30 to 50% in elderly patients. The relative decrease with age becomes greater following salt restriction, diuretic therapy, or upright posture.

Postural hypotension is frequent in elderly individuals and may be exacerbated by many drugs. The pathogenesis is probably multifactorial and includes decreased baroreceptor response, altered sympathetic activity and responsiveness, impaired vasomotor response in both arterioles and veins, and altered volume regulation. Phenothiazines, tricyclic antidepressants, levodopa, antihypertensive drugs and diuretics are frequent causes of postural hypotension seen in clinical practice.
ADVERSE DRUG REACTIONS IN ELDERLY

The incidence of adverse drug reactions in elderly is 2-3 times more than that seen in young adults. It is seen more between ages of 61-80 yrs. The most consistent risk factor for adverse drug reactions is number of drugs being taken. Risk of adverse drug reactions rises exponentially as the number of drugs increases.

Commonly used drugs which produce unwanted effects in elderly:

1. Postural Hypotension: Isosorbide dinitrate, TCA, Levodopa, antipsychotics, β blockers, diuretics, α blockers.
2. Constipation: Anticholinergics, antidepressants, antipsychotics, opioids, nifedipine
3. Urinary Incontinence: Antipsychotics, β blockers, diuretics, prazosin, lithium, labetalol

COMMON DRUG INTERACTIONS

Age-related pharmacokinetic and pharmacodynamic changes can potentially increase the risk of adverse events from drug interactions. Cellular, organ, and systems reserves decrease with age. The effects of individual genetics, lifelong living habits, and environment will result in heterogeneity between people as they age24-27.

Some common drug interactions associated with their risk are listed in Table III

<table>
<thead>
<tr>
<th>Table 3: Common examples of drug combinations associated with their risk in old age.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Combination</strong></td>
</tr>
<tr>
<td>ACEI + Diuretics</td>
</tr>
<tr>
<td>ACEI + Potassium</td>
</tr>
<tr>
<td>Antiarrhythmic + Diuretic</td>
</tr>
<tr>
<td>BZD + antipsychotics / antidepressants</td>
</tr>
</tbody>
</table>

Some examples of medicines commonly needed in geriatric age group, drugs to be avoided with their reasons and the safer alternatives are discussed in Table IV

<table>
<thead>
<tr>
<th>Table 4: Drugs to be avoided in geriatric age group, the reason to be avoided and their safer alternatives.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drugs to be avoided</strong></td>
</tr>
<tr>
<td>SEDATIVES and HYPNOTICS Chlordiazepoxide</td>
</tr>
<tr>
<td>Diazepam</td>
</tr>
<tr>
<td>Barbiturate</td>
</tr>
<tr>
<td>Flurazepam</td>
</tr>
<tr>
<td>ANALGESICS Opioids</td>
</tr>
<tr>
<td>NSAIDS</td>
</tr>
<tr>
<td>ANTIPSYCHOTICS Phenothiazine Haloperidol</td>
</tr>
<tr>
<td>ANTIDEPRESSANTS Tricyclic antidepressants</td>
</tr>
<tr>
<td>ANTIMANIA Lithium</td>
</tr>
<tr>
<td>ALZHEIMER’S DISEASE Tacrine (Cholinesterase inhibitor)</td>
</tr>
<tr>
<td>GENERAL ANAESTHETICS Halothane Enflurane Thiopentol</td>
</tr>
<tr>
<td>ANTIHYPERTENSIVE DRUGS Thiadizide diuretics in high doses Methyldopa Beta-Blockers</td>
</tr>
</tbody>
</table>
CARDIAC GLYCOSIDES
Increase in sensitivity to the toxic antarrhythmic actions of digoxin. Clearance of digoxin is usually decreased and its half life is prolonged.
Loading doses should be reduced and maintenance dose should also be reduced.

ANTIARRHYTHMIC DRUGS
Quinidine
The clearance of quinidine is decreased and its half life is prolonged in elderly. Half life of Xylocaine is also increased in elderly, toxic effect more.
Quinidine and Xylocaine can be used with reduced doses.

Xylocaine

ANTIMICROBIAL AGENTS
Penicillin
Cephalosporins
Aminoglycosides
Due to decrease in renal function half life of these drugs prolonged.
Aminoglycosides causes nephrotoxicity. (reversible)
According to some studies, half life of Tobramycin is not prolonged.
Use of ceftriaxone and cefoperazone which are excreted through bile. Otherwise dose adjustment.

LAXATIVES and PURGATIVES
Castor oil
Liquid paraffin
Damage to intestinal mucosa. Small amount may pass into intestinal mucosa to produce foreign body granulomas.
Prefer Ispaghula, bran, Bisacodyl.

ANTIEMETICS
Metoclopramide
Avoided due to its extra pyramidal side effects.
Prefer domperidone or ondansetron.

ANTIDIABETIC DRUGS
Chlorpropamide
Glibenclamide
Half life of these drugs gets increased in elderly.
These are known to cause serious side hypoglycemia episodes.
Glipizide and gliclazide may be used.

PRINCIPLES OF PRESCRIBING DRUGS FOR ELDERLY PATIENTS
The following questions are to be answered carefully before prescribing drugs to elderly patients:

- Is drug therapy required?
- If drug treatment is required, which drug is appropriate?
- Is the patient being asked to take more drugs than are tolerable or manageable?
- Which type of preparation should be used?
- Should the standard dosage or dosage schedule be modified?
- Should the drug be specially packaged and labeled?
- Can the patient living at home manage self medication?
- Is there a need for continued medication?
- Is the drug affordable?

Many of the diseases which elderly patients experience either do not require treatment or are not effectively treated with available medications. Many old people admitted to hospital or reviewed during long term hospitalisation improve greatly when the regimen of drugs that they have been taking is stopped. These edicts do not mean, however, that drugs should be withheld on account of old age, particularly when appropriate drug treatment can improve the elderly person’s quality of life.

The margin between therapeutic effect and toxicity is so small in many cases that a drug which is indicated for a particular condition in younger patients may be unsuitable in elderly patients with the same condition. For example, the age-related toxicity of benzodiazepines with long half-lives has made the use of these drugs undesirable in elderly patients.

The smallest number of drugs that the patient actually needs should always be used. The likelihood of toxicity increases as the number of drugs prescribed rises. Medication errors, especially errors of omission, non-comprehension and non-compliance with medication instructions, have long been recognised as occurring in elderly patients.

The dosage form and the size, shape and colour of tablets and capsules, and their similarity to one another are all important considerations in prescribing drugs to elderly patients. Many older people have difficulty in swallowing; consequently, large tablets and capsules should be avoided. There is a good case for the use of liquid preparations such as syrups for many patients, or of effervescent tablets. On occasion, suppositories may be the most suitable method of administration.

Whenever possible, intermittent schedules such as drugs given on alternate days or 5 days a week should be avoided, since they are rarely followed accurately. Once-daily dosage ensures better compliance than more frequent regimens. Apart from convenience to the patient and better compliance, once daily dosage at night, for example of psychotherapeutic drugs, may decrease troublesome adverse reactions since the patient would be asleep when these effects would be most annoying.

Where possible, drugs prescribed for elderly patients living at home should be packaged in readily opened containers so that disabled patients in particular are able to use them. Clear labeling in large print is also very important. Blister packaging or unit dose packaging can reduce non-compliance significantly.

Elderly patients should be taught to understand the drugs they must take, particularly the relative importance of drugs to their well-being. Time should be spent to educate the patient in the use and administration of their regimen. Sometimes it may be necessary to provide clear instructions in writing about the manner in which a drug should be taken or to suggest the use of a diary or calendar to record daily drug administration.

When a drug such as digoxin has been prescribed in an acute episode (e.g. atrial fibrillation complicating pneumonia) there may be no reason for its continued use once the acute episode is satisfactorily treated. It is useful to review treatment regularly and discontinue drugs that are no longer needed.

Cost-effectiveness is a very important parameter that should be kept in mind while prescribing drugs to the elderly.

POLYPHARMACY IN THE ELDERLY
Polypharmacy means "many drugs" or the use of more medication than is clinically indicated or warranted, or the empirical use of five or more medications. It is surveyed that average use of medicines for persons above 65 years of age are 2 to 6 prescription drugs and 1 to 3.4 over-the-counter medicines. Polypharmacy leads to more adverse drug reactions and decreased adherence to drug regimens.
Patient outcome is also affected, constituting of poor quality of life, high rate of symptomatology and (unnecessary) drug expense.

The factors that may contribute to polypharmacy though underreported are use of multiple health care providers and others’ medications by geriatric patients and limited time for discussion and consultation.
Role of Care Provider in Polypharmacy

At least yearly, and more often if indicated, ask elderly patients to bring in all medications they have at home including their prescription, over-the-counter medicines, vitamins supplements, herbal preparations, etc. The use of vitamins and herbal products in elderly people is very common and generally not reported to the physician. Some serious drug interactions are possible, e.g. with Warfarin, gingko biloba, vitamin E.

What should a care provider do with the 'Brown Bag full of bottles'? He should document and determine indication, prioritize vital vs. optional and cure vs. relieve symptom drugs, discuss with the patient and caregiver, plan for medication reduction. Discontinuing unnecessary medications is one of the most important aspects of decreasing polypharmacy. Drugs without indications should be stopped.

REFERENCES

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