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GERIATRIC PHARMACOTHERAPY AND MEDICATION ADVERSE EFFECT: A REVIEW

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Pharmacotherapy or drug therapy, is defined as medical treatment that utilizes one or more pharmaceutical drugs to improve illness symptoms relief, treat the underlying condition, or act as a prevention for other diseases.[1] Pharmacotherapy is an important health care therapy in preventing illness, disability and death in geriatric population and improve quality of life. Pharmacotherapy in geriatric patients is difficult and complicated task for physician. 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 can contribute to adverse drug reactions and has been found to be a frequent cause of hospitalization and morbidity.[2] As a person ages, there are many normal physiological changes that take place which may affect the way in which a person processes and responds to medications. Aging is characterized by a gradually developing loss of functioning of most of organs, a reduction in homeostatic mechanisms, and a response to receptor stimulation. Also occur loss of water content and an increase of fat content in the body. Therefore, understanding the influence of age-dependent changes in functioning of the body on the pharmacokinetics and pharmacodynamics of drugs is important criteria before prescribing drugs to elderly patients. In geriatric patients changes in Pharmacokinetic and pharmacodynamic sensitivity affect the drug therapy.

Pharmacokinetics in geriatric patients

Pharmacokinetics refers to what the body does to a drug. it involve drug absorption, distribution, metabolism and excretion.[3] With aging, there are changes in all these areas; some changes are more clinically relevant. The metabolism and excretion of many drugs decrease, requiring that doses of some drugs be decreased. Toxicity may develop slowly

because concentrations of chronically used drugs increase for 5 to 6 half-lives, until a steady state is achieved.

Absorption

Absorption of drugs as well as nutrients altered because with age, there is reduced digestive secretions like gastric, pancreatic, bile and intestinal secretion. Also decrease in small-bowel surface area, slowed gastric emptying, and an increase in gastric pH leads to changes in drug absorption.[3]

Distribution

With age, body fat generally increases and total body water decreases. Increased fat increases the volume of distribution for highly lipophilic drugs (diazepam) and may meaningfully increase their elimination half-lives.

Metabolism

As people age, there are several changes in hepatic (liver) metabolism that can impact drug handling and overall health. Hepatic metabolism of many drugs through the cytochrome P-450 enzyme system decreases with age. For drugs with decreased hepatic metabolism clearance typically decreases 30 to 40%.

Renal elimination

One of the most important pharmacokinetic changes associated with aging is decreased renal elimination of drugs. After age 40, glomerular filtration rate (GFR) decreases an average of 8 mL/min/1.73 m^2/decade (0.1 mL/sec/m^2/decade); however, the age-related decrease varies substantially from person to person. Serum creatinine levels often remain within normal limits despite a decrease in glomerular filtration rate (GFR) because older adults generally have less muscle mass and are generally less physically active than younger adults and thus produce less creatinine. Maintenance of normal serum creatinine levels can mislead clinicians to assume those levels reflect normal kidney function. Decreases in tubular function with age parallel those in glomerular function.[3]

Pharmacodynamic in geriatric patients

Pharmacodynamic is study of biochemical and physiologic effect of drug or is defined as what the drug does to the body or the response of the body to the drug. In older adults, the effects of similar drug concentrations at the site of action (sensitivity) may be greater or

smaller than those in younger people. Differences may be due to changes in drug-receptor interaction, post receptor events, or adaptive homeostatic responses and pathologic changes in organs. as the age increases drug sensitivity decreases.[4]

Age related disease and their medications related adverse effect

Antihypertensive

Hypertension in older adults is related to adverse cardiovascular outcomes, such as heart failure, stroke, myocardial infarction, and death. Hypertension is increasing due to an aging population and increasing prevalence of obesity. Arterial stiffness is the major cause of elevated systolic blood pressure and pulse pressure as well as lower diastolic blood pressure in older adults. These age-related alterations are powerful determinants of major cardiovascular disease and all-causes of mortality. This is challenge to physician to prescribe appropriate Antihypertensive medicines with as possible as lower side effect. When medications are needed to manage older adults with uncontrolled hypertension, factors should be considered prior to selecting a medication include comorbidities, ability to follow instructions, complexity of the current regimen, frailty of the patient and electrolytes and renal function.[5][6]

Pharmacologic interventions

Calcium channel blockers dihydropyridine, Loop diuretic thiazide, ACE inhibitors, Angiotensin II receptor antagonists, β- adrenoreceptor antagonists (β-blockers), Aldosterone antagonists, α-adrenoreceptor antagonists (α-blockers), Central α-adrenoreceptor agonists have all show benefit on hypertension in older age patients. But these drugs also showing some adverse effect in elderly patient which to be concern.[3][4]

Adverse effect of anti-hypertensive drugs and considerations for individualization of drug therapy

Aldosterone antagonists show hyperkalaemia, hyponatremia, and gastrointestinal disturbances, including cramps and diarrhoea, gynecomastia in old patients.

Aldosterone antagonist should not be given in instances of severe renal insufficiency, estimated creatinine clearance <30 mL (min·1.73 m^2) or hyperkalaemia. Creatinine and electrolyte monitoring is warranted after each dose change.

A-adreno receptor antagonists (α-blockers) shows Dizziness, fatigue, nausea, urinary incontinence, orthostatic hypotension, syncope. Usually not indicated. Risk of hypotension (orthostatic, postprandial) and syncope.

ACE inhibitors show dry cough, hyperkalaemia, rash, angioedema, dizziness, fatigue, acute renal failure.to avoid these complication ACE inhibitors have been tested in the only RCT specific for subjects >80 y. Avoid if you suspect dehydration, do not simultaneously increase diuretics to avoid a worsening in renal function. Regular control of creatinine and potassium levels.

Angiotensin II receptor antagonists exert Hyperkalaemia, rash, dizziness, fatigue, sometimes acute renal failure in some people. Do not combine ARB with ACE inhibitor or renin inhibitor. Be cautious with aldosterone antagonist because of increased risk of hyperkalaemia.

Calcium channel blockers show some common side effect like Signs related to sympathetic activation like flushing, headache, tachycardia, lower limb oedema, bradycardia, AV block, worsening heart failure, constipation, fatigue and dyspnoea. Diltiazem can also cause lower limb oedema. With verapamil, lower limb oedema is unusual, but constipation may be a major problem in very old individuals, as it can lead to faecal impaction, with nausea, anorexia, delirium, and functional decline.so never combine verapamil with β-blockers.

Diuretics like Thiazides which is loop diuretic showing adverse effect such as hyponatremia, hypokalaemia, hyperuricemia and gout attacks, hypotension, and dehydration. Diuretic should be titrated according to the patient's volemic status. Creatinine and electrolyte monitoring is warranted after each dose change. Loop diuretics are not indicated for hypertension unless there is severe renal insufficiency. In the presence of both hypertension and heart failure, loop diuretics can be used for both diseases, either alone or in combination with thiazides.[5][6]

Antidiabetics

Diabetes is a disorder of glucose metabolism. It is not appreciated, however, that glucose metabolism varies with age in normal individuals as well. Glucose homeostasis, or balance, depends upon adequate insulin secretion from the pancreas and appropriate sensitivity of insulin receptors to the hormone. Both insulin secretion and insulin sensitivity are impaired with increasing age. Various factors frequently encountered in old age contribute to, or are

associated with, insulin resistance. These include central obesity, induced by various environmental factors, secretion of arginine vasopressin or its C-terminal fragment. Vitamin D deficiency and hypomagnesemia have also been incriminated in the pathogenesis of diabetes in the elderly. Age-related changes in kidney and liver function are the most important physiological changes to consider when selecting an appropriate diabetes regimen for older adults. The progressive decline in renal function that occurs with age may result in slower elimination of drugs that are partially or completely cleared by the kidneys, including metformin and other diabetes agents. Additionally, some drugs are metabolized to active metabolites that are eliminated by the kidneys (e.g., some sulfonylureas) and can build up within the body, leading to toxicity and additive side effects if dosages are not adjusted. Higher serum concentrations may result in greater risk of hypoglycaemia when such drugs are used.[7]

Pharmacologic interventions

Insulin, oral hypoglycaemic agents like sulfonylureas, non-sulfonylureas, alpha glucosidase inhibitors, biguanides and thiazolidinedione are recommended for treatment of diabetes in geriatric patients.[8]

Adverse effect of antidiabetic drugs and considerations for individualization of drug therapy

Biguanides like metformin should be avoid in hepatic impairment. It increases the risk of lactic acidosis associated with metformin. Use should be avoided in elderly patients unless normal renal function.it also causes deficiency of vitamin B12. Metformin dose should be adjusted if patient taking Amiloride, Cephalexin, Digoxin because these drugs interfere with the enzyme to which metformin used to its activity.

Glimepiride initiate therapy conservatively, maintain based on clinical response. An upset stomach, skin rashes are some common side effects but it contraindicated with others drug like azole antifungals, antibiotics like chloramphenicol, isoniazid, rifampin, sulfasalazine etc.[9]

Glyburide increases risk of hypoglycaemia. Avoid use of glyburide if creatinine clearance is <50 ml/min.

Thiazolidinedione is insulin sensitizer that act on intracellular metabolic pathway to enhance insulin action and increase insulin sensitivity.[10]

It is linked to a few serious side effects, including bone fracture, heart failure and bladder cancer in women. Liver damage also reported.

Consideration of drug therapy

Factors related to patients	Drug preference
Renal failure	Thiazolidinedione, Glinides, Insulin
Hepatic disease	Glinides, Alpha glucosidase inhibitors, Insulin
Frequent hypoglycemia	Metformin, Thiazolidinedione, Glinides, Insulin
Obesity	Metformin, Alpha glucosidase inhibitors

Anticoagulants

For patients with atrial fibrillation (AF) or venous thromboembolism (VTE) undergoing percutaneous coronary intervention (PCI) or with atherosclerotic cardiovascular disease (CAD), a combination of oral anticoagulation (e.g., direct oral anticoagulants - DOACs) and P2Y12 antiplatelet therapy is recommended. Management of anticoagulation in elderly patients represents a particularly challenging issue. The different steps physicians have to go through for prescribing anticoagulants are all highly challenging when it comes to taking care of elderly patients. The management of different anticoagulant molecules needs particularly careful attention in the elderly in order to avoid adverse effects.

Pharmacologic interventions

Vitamin K Antagonists (VKA), Synthetic Pentasaccharides (Fondaparinux, Idraparinux), Unfractionated Heparin (UFH), Low Molecular Weight Heparins (LMWH), Thrombin (Factor IIa) Inhibitors prescribed as anticoagulant in elder patients.

Adverse effect of anticoagulant drugs and considerations for individualization of drug therapy

Unfractionated Heparin (UFH) used as anticoagulant in elder patients have risk of heparin-induced thrombocytopenia, an antibody-mediated adverse reaction to heparin-platelet factor 4 complexes associated with a high risk of thrombosis. Intracranial haemorrhage is one of the most feared complications of this therapy as it is a serious condition associated with a substantial increase in mortality.[11]

Low Molecular Weight Heparins (LMWH), Low molecular weight heparins are glycosaminoglycans. They are derived from various processes of depolymerization of UFH. The main concern when prescribing LMWHs in elderly patients is renal impairment. Particular attention is therefore needed in the elderly using the Cockroft-Gault formula should be calculated in these patients before prescribing LMWHs.

Vitamin K Antagonists (VKA) Warfarin is the most widely prescribed VKA. It shows anticoagulant effect by interfering with vitamin K metabolism. Vitamin K is involved in bone metabolism, so it has been hypothesized that vitamin K antagonists (VKAs) would increase the risk of fracture.[12] Various studies have evaluated fracture risk with long-term VKA therapy. When introducing VKAs in elderly patients, their higher sensitivity to these medications should be taken into account, and lower initial doses should be prescribed.[13][14][15]

Intracranial haemorrhage is one of the most feared complications for this therapy. Apixaban is associated with the lowest risk of bleeding and is likely to be the preferred option.[11]

Dementia

Dementia is a term used to describe clinical syndromes associated with irreversibly progressive deterioration of multiple higher cortical functions, including language, memory, calculation, comprehension, thinking, learning skills and appropriate judgment, leading to interfering with functional ability and daily life.[16],[17] Due to the deterioration of cortical functions, especially in memory, people with dementia may take the medicine repeatedly or wrong medications, resulting in drug related problems (DRPs) and increased medication use. These problems have devastating effects on health outcomes, such as adverse drug events, morbidity and mortality. Most geriatric patients with dementia usually consume a mean of five or more medications, commonly defined as polypharmacy (PP).[18],[19] Although taking multiple medications may be necessary for the management of dementia and chronic diseases, the use of multiple medications can lead to greater risk of DRPs, including potentially inappropriate medications (PIMs), drug-drug interactions (DDIs), and adverse drug reactions (ADRs). Apart from polypharmacy, age-related pharmacokinetic and pharmacodynamics changes can cause higher risk for undesirable DRPs. older people with dementia have an alteration of blood-brain permeability and levels of endogenous neurotransmitters which may increase their sensitivity to neurological effects of medications, leading to greater experience of ADRs.

Pharmacologic interventions

Cholinesterase inhibitors act by inhibiting cholinesterase enzyme and increasing acetylcholine, a chemical messenger in brain that aids in memory and judgment. Increasing the amount of acetylcholine in brain may delay symptoms of dementia e.g. Galantamine, Donepezil, Rivastigmine etc. Amyloid beta-directed antibody like Lecanemab. Orexin antagonist Suvorexant used in dementia related symptoms such as insomnia.

Adverse effect of drugs and considerations for individualization of drug therapy

Cholinesterase inhibitors concerning adverse effects include prolonged muscle contraction, GI disturbances, insomnia, headedness, weakness and weight loss.

Lacenemab is an Amyloid beta directed antibody cause amyloid-related imaging abnormalities. It causes swelling of the brain, confusion, dizziness, vision changes, nausea and seizure. Suvorexant, is an orexin antagonist medication shows adverse effect include sleep paralysis, somnolence, dry mouth, sleep-related hallucination, complex sleep behaviour like sleepwalking, and suicidal ideation may occur. Brexpiprazole is an atypical antipsychotic drug exert akathisia The most common side effects among people with agitation associated with dementia include headache, dizziness, urinary tract infection, nasopharyngitis, and sleep disturbances.[21][22]

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