MANAGING DRUG REGIMENS IN OLDER PATIENTS WITH CKD

With increasing age, organ function, lean body mass, serum albumin, blood flow to the liver and glomerular filtration rate (GFR) tends to decline. A reduction in GFR can have significant consequences on drug metabolism and excretion. This can enhance adverse drug reactions, especially in the elderly population who often have accompanying comorbidities. Planning a therapeutic drug regimen in such patients is difficult because of the scarcity of information available on the pharmacokinetic and pharmacodynamic properties of drugs routinely used in this patient population. To further complicate matters, many elderly patients suffer from inadvertent poor compliance. This issue of CLIPS briefly summarizes an article that addresses issues regarding the use of drugs in older adults with chronic kidney disease (CKD) and provides some recommendations to reduce the risk of adverse drug reactions. If you need further information, please contact the Samford University Drug Information Service at (205) 726-2659.


Pharmacokinetic Profiles

- Absorption can be impaired by the use of proton pump inhibitors, severe hypoalbuminemia, and gastrointestinal disorders.
- Lipophilic drugs may have an increased volume of distribution and a prolonged half-life. Conversely, age-related decrease in GFR may reduce the elimination of water-soluble drugs. Thus, reduced dosages of lipophilic and hydrophilic drugs are suggested in older patients with CKD.
- In patients with hypoalbuminemia, drugs that are highly protein bound will circulate free in the plasma at higher percentages and will have an increased volume of distribution.
- Hepatic metabolism renders lipophilic compounds more hydrophilic enabling them to be excreted by the kidneys. It also converts inactive drugs to active drugs, and vice versa. These processes become impaired with aging and contribute to an increase in the half-life of lipophilic drugs. Consequently, the dose of hepatically metabolized drugs should be reduced in older patients with CKD, especially in patients with a GFR less than 30 mL/min, and then gradually titrated upward.
- Kidneys regulate the elimination of hydrophilic drugs. The GFR decreases steadily after the age of 30 years and even more rapidly after the age of 65 years. In patients with CKD and decreased GFR, the initial dose of water-soluble, non-protein bound drugs is unchanged. However, the interval between dosing must be changed to maintain safe and effective blood levels.

Pharmacodynamic Profiles

- The aging process may dramatically affect the union of a drug to its receptor, thereby altering the drug’s response.
- Elderly patients can have altered responses to some cardiovascular drugs including decreased tolerance to vasodilators and dihydropyridine calcium channel blockers (CCBs) show an increased effect (e.g., gingival hypertrophy and peripheral edema). Also, the reduced elimination of digoxin increases the risk of sinoatrial block, tachycardia, and ventricular fibrillation.
- Drugs that affect brain function such as anesthetics, opioids, anticonvulsants, psychotropic agents, and sedative hypnotic drugs should be used cautiously.

Specific Issues in Older Adults with CKD

- Renin-Angiotensin-Aldosterone Antagonists can increase the serum level of potassium and decrease the GFR. Concomitant administration of a loop diuretic or potassium-sodium ion-exchange resin may be helpful.
- The dosage of fluoroquinolones should be adjusted according to eGFR. Fluoroquinolones can cause confusion, weakness, tremor, or depression. This class can also cause QT prolongation and tendonitis or tendon ruptures.

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Specific Issues in Older Adults with CKD (continued)

- After the first dose of an aminoglycoside, the dosage should be modified by dose reduction or dosing interval prolongation in order to avoid renal and ear toxicity. Peak and trough levels should be monitored at least twice a week if renal function is unstable. Monitor for signs and symptoms of toxicity.
- Trimethoprim-Sulfamethoxazole may cause rash, fever, neutropenia, thrombocytopenia, and transaminase (liver enzyme) elevation. Also, it can increase the risk of high potassium and phenytoin toxicity.
- Clarithromycin and erythromycin strongly inhibit CYP3A4 and can lead to the accumulation of CCBs which can cause bradycardia and heart block. It can also increase the risk of muscle damage in patients taking statins.
- Drugs such as TMP-SMX and amiodarone can inhibit CYP2C9 and increase the anticoagulant effect of warfarin while rifampicin, carbamazepine, and barbiturates have the opposite effect.
- The concurrent use of oral anticoagulants and NSAIDs increases the risk of hemorrhagic peptic ulcers.
- Calcium supplementation can reduce the absorption of other drugs. Also, their long-term use may result in vascular calcifications. Calcium intake should not exceed 1 g/d.
- Lithium use can cause acute or chronic kidney failure and nephrogenic diabetes insipidus, particularly in older adults. Concurrent use of a loop diuretic and ACEI can increase this risk and should be used cautiously.
- Antihyperglycemic drugs should be titrated carefully due to the risk of hypoglycemia (especially with sulfonlureas). Metformin-induced lactic acidosis is rare but the risk increases proportionally with the degree of renal impairment and patient age. Metformin is not considered safe if the eGFR is below 30 mL/min. SGLT2 inhibitors (e.g., canagliflozin, dapagliflozin) are well tolerated and are an alternative for patients who are not well controlled with metformin.
- Antihypertensives should be started at a low dose to mitigate fall risks. β-Blockers should be used with caution in patients older than 60 years and immediate-release nifedipine should not be given to older patients.
- Statins help reduce proteinuria, suppress oxidative stress, and improve endothelial function in CKD. They also reduce LDL cholesterol which helps decrease the incidence of major atherosclerotic events in patients with advanced CKD. A systematic review reported that statins consistently lower death and major CV events by 20% in people with CKD not requiring dialysis. Caution should be used in patients older than 85 years.
- NSAIDs can lead to renal vasoconstriction and reversible reduction of kidney function. This risk is increased by the concurrent use of diuretics or ACEIs.
- Long term therapy with proton pump inhibitors (PPIs) is associated with fractures, enteric infections, impaired physical and cognitive functioning, hypomagnesemia, and acute kidney injury.
- SSRIs are known to cause some psychological and GI ADRs, but they may also cause severe hyponatremia which can be particularly pronounced in patients undergoing peritoneal dialysis.

Adherence to Prescriptions

- Poor adherence to medications is a common problem in older individuals.
- Polypharmacy is a major factor that contributes to nonadherence.
- New onset ADRs can be mistaken as new-onset disease or morbidity related to aging.
- OTC dietary supplements and herbals that are often taken by the elderly can cause drug interactions.

Summary

- Developing an effective therapeutic regimen in aged patients with CKD is challenging for a number of reasons including; paucity of information is available regarding the pharmacokinetics and pharmacodynamics of certain drugs in the setting of CKD, especially of those with a narrow therapeutic index; and this treatment population is characterized by unintentional poor adherence to drug regimens.
- Some steps may be taken to reduce the risk of adverse effects include: reducing the initial dose of drugs; using a limited number of drugs; simplifying treatment regimen and number of daily doses; making sure patients understand their medications and the appropriate way to take them; checking renal function regularly; ensuring good communication with the patient.

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