Review Article

Mini review on potentially reported adverse effects of drugs used for chronic kidney disease

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ABSTRACT

Chronic kidney disease (CKD) is a progressive, irreversible decline in renal function in which body's ability to maintain metabolic and fluid and electrolyte balance fails, resulting in uremia or azotemia. It is not a single disease and associated with different medical conditions such as diabetes, hypertension, and anemia; even though it is caused by primary kidney disease (e.g., glomerular diseases, tubulointerstitial diseases, obstruction, and polycystic kidney disease). This paper provides different stages of CKD estimated based on glomerular filtration rate and provides drug treatment used for CKD with their adverse effects. It also provide brief about treatment of end-stage kidney disease.

Keywords: Acute kidney injury, Chronic kidney disease, Parathyroid hor mone, Vitamin D receptor antagonists

INTRODUCTION

Chronic renal failure (CRF) is a global public health crisis that tends to take dimensions of epidemic and has severe impact on quality of patient's life.[1] It is a progressive, irreversible deterioration in renal function in which the body's ability to sustain metabolic and fluid and electrolyte balance fails, resulting in uremia or azotemia (retention of urea and other nitrogenous wastes in the blood).[2] The kidneys regulate the composition and volume of blood, remove metabolic wastes in the urine, and help control the acid/ base balance in the body. It is typically a progressive disease and is defined as; reduction of kidney function-defined as an estimated glomerular filtration rate (GFR) <60 mL/min/1.73 m^2 and/ or evidence of kidney damage, including persistent albuminuria-defined as >30 mg of urine albumin per gram of urine creatinine. It is virtually always asymptomatic in its early stages.[3,4] It is not a single disease. It is categorized by the level of kidney function, based on GFR, into Stages 1–5, with each increasing number indicating a more advanced stage of the disease, as defined by a declining GFR [Table 1]. This classification system from the National Kidney Foundation's Kidney Dialysis Outcomes and Quality Initiative (K/DOQI) also accounts for structural evidence of kidney injuries.[5-7]

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CHRONIC KIDNEY DISEASE (CKD)-RELATED COMPLICATIONS

Most patients with CKD will die of events related to cardiovascular disease before ESRD develops.6'7Therefore, an important focus of care for patients with CKD includes management of cardiovascular risk factors. Progression of CKD is associated with a number of serious complications and the potential complications of CRF that concern the health professional and that necessitate a collaborative approach to care include; hyperkalemia (due to decreased excretion, metabolic acidosis, and catabolism) and excessive intake (diet, medications, and fluids); pericarditis, pericardial effusion, and pericardial tamponade due to retention of uremic waste products, and inadequate dialysis; and hypertension due to sodium and water retention and malfunction of the renin-angiotensin-aldosterone system.[8]

TREATMENT OF CKD

- Depending on the underlying cause, some types of kidney disease can be treated. Often, though, CKD has no cure
- Treatment usually consists of measures to help control signs and symptoms, reduce complications, and slow progression of the disease. If your kidneys become severely damaged, you may need treatment for end-stage kidney disease (ESKD).

Table 1: Stages of chronic kidney disease based on kidney function estimated by glomerular filtration rate[3]

Stages	Description	GFR	Related terms
		Ml/min/1.73 m^2	
1	Kidney damage with normal or ↑ GFR	≥90	Albuminuria, proteinuria
2	Kidney damage with mild ↓ GFR	60–89	Albuminuria, proteinuria
3	Moderate ↓ GFR	30–59	Early or chronic renal insufficiency
4	Severe ↓ GFR	15–29	Late or chronic renal insufficiency, pre-end-stage kidney disease
5	Kidney failure	<15 (or dialysis)	Renal failure, uremia, end-stage kidney disease

GFR: Glomerular filtration rate

DRUGS FOR TREATMENT WITH ADVERSE EFFECTS

Diuretics

Thiazide and loop diuretics are commonly used for natriuresis and blood pressure (BP) control with a reduced GFR. This is especially important in advanced CKD, where extracellular volume excess is a concern and BP becomes more salt-sensitive. Loop diuretics are the preferred agents at GFR, 30 ml/min/1.73 m^2, but more potent thiazide diuretics also can be used, often in combination with loop diuretics. Injudicious diuretic use can increase the risk of AKI in vulnerable patients with CHF.

Adverse effects

Loop and thiazide diuretics are also associated with a range of electrolyte disturbances, including hypokalemia, hypomagnesemia, and hypochloremic metabolic alkalosis.[9,10] Additional metabolic derangements include hyperuricemia, and at higher doses of thiazide diuretics, glucose intolerance, and hyperlipidemia.[11]

RAAS blockers as a double-edged Sword

RAAS blockers are essential to CKD treatment. RAAS blockers have demonstrated benefit in early as well as later stages of CKD.[12,13]

Adverse effects

Most in conditions where the kidney is autoregulation-dependent, including CHF, active diuresis, and other illnesses with attendant volume depletion.[12] Hypotension with RAAS blockers is common among elderly patients.[14] AKI is also more common with treatment with RAAS blockers during high summer temperatures and with volume depletion and can also occur with bilateral renal artery stenosis or unilateral stenosis with a solitary kidney.[15] Adding a nonsteroidal anti-inflammatory drug (NSAID) to an RAAS blocker and diuretic can amplify the risk of AKI and has been described as a triple whammy.[16] Similar conditions may increase the risk of AKI when more than one RAAS blocker are used together, or in combination with sodium-glucose cotransporter 2 in patients with CKD and diabetes.[17,18] AKI admissions increased as much as 15% because of an increase in RAAS blocker prescriptions.[19]

Dyskalemia

Hyperkalemia and hypokalemia are common concerns with CKD because they can lead to altered cardiac electro-conduction, arrhythmias, and sudden death.[20-25] Hyperkalemia can occur with RAAS blocker use, especially when two are used in combination, or with other drugs including potassium-sparing diuretics, NSAIDs, or trimethoprim-sulfamethoxazole.[26] Dialysis remains the gold standard for potassium removal, but should be used sparingly, except for patients with ESKD. Treatment and prevention of hypokalemia include reduction in diuretic use, sodium restriction, and liberalization of patient's diets to include potassium-rich foods. Consideration of potassium-sparing diuretics and RAAS blockers, where appropriate, should also be considered.[27]

Treatments for anemia in CKD

Anemia management in CKD is a balance between optimizing erythropoiesis and minimizing adverse effects associated with therapeutic agents that treat anemia.[28,29] Use of erythropoiesis-stimulating agents (ESAs) along with iron supplementation to treat anemia is important elements in CKD care. Iron supplementation (oral or intravenous) is usually the first step in anemia management.[30] However, oral iron use is often limited because of suboptimal efficacy and gastrointestinal intolerance. Intravenous iron is more efficacious at correcting iron deficiency, improving hemoglobin levels, and reducing ESA use and blood transfusions, but is often underutilized because of clinician apprehension of infusion related reactions and iron overload.[31,32]

Adverse effects

Anaphylaxis most commonly occurs with high molecular weight iron dextran, whereas severe or life-threatening reactions are rare with non-dextran formulations, such as iron sucrose and sodium ferric gluconate complex. The upper limits of iron stores are clinically undefined, but studies suggest that adverse effects related to iron overload are not likely to occur at ferritin levels below 1200–2000 ng/ml.[33]

Treatments for CKD mineral and bone disorder (MBD)

CKD–MBD is a complex condition characterized by phosphate, calcium, Vitamin D, and parathyroid hormone (PTH) abnormalities.[34] Drug therapy for CKD–MBD has the potential to accelerate disease progression if not used appropriately. Phosphate binders are the recommended first-line therapy in CKD to correct hyperphosphatemia.[35]

Adverse effects

Calcitriol and other Vitamin D receptor antagonists (VDRA) suppress parathyroid gland activity in advanced stages of CKD. However,

there may be a negative shift in the risk benefit profile for VDRAs in predialysis CKD because their use is associated with increased risk of hypercalcemia with no significant benefit to cardiac function. Calcimimetics are also efficacious at suppressing PTH secretion in CKD–MBD.[36,37] This class of agents is commonly associated with hypocalcemia in patients with ESKD and patients who are predialysis.

Antihyperglycemic agents in CKD

Poorly controlled type 2 diabetes (T2DM) mellitus can lead to microvascular complications, including nephropathy, as 40% of patients with T2DM have CKD. Metformin remains the first-line treatment for T2DM.[38,39]

Adverse effects

Metformin was contraindicated in patients with a serum creatinine level of >1.5 or >1.4 mg/dl for men and women, respectively, given that the drug is eliminated through the kidneys and can increase the risk of lactic acidosis.[40]

Anticoagulant agents in CKD

Many patients with CKD require anticoagulation for comorbid conditions and treatment with Vitamin K antagonist or direct oral anticoagulants (DOACs). Although all DOACs can be used with impaired kidney function, the recommendations for dose adjustment are dependent on indication and kidney function. Low molecular weight heparin should also be administered at a reduced dose with lower GFRs and avoided in ESKD.[41]

TREATMENT OF ESKD

- If kidneys cannot keep up with waste and fluid clearance on their own and develop complete or near-complete kidney failure, have ESKD. At that point, need dialysis or a kidney transplant.

Dialysis

Dialysis artificially removes waste products and extra fluid from blood when kidneys can no longer do this. In hemodialysis, a machine filters waste and excess fluids from blood. In peritoneal dialysis, a thin tube (catheter) inserted into abdomen fills abdominal cavity with a dialysis solution that absorbs waste and excess fluids. After a period of time, the dialysis solution drains from body, carrying the waste with it.

Kidney transplant

A kidney transplant involves surgically placing a healthy kidney from a donor into recipient body. Transplanted kidneys can come from deceased or living donors. Recipient needs to take medications for the rest of your life to keep body from rejecting the new organ. Do not need to be on dialysis to have a kidney transplant.[42]

DISCUSSION

Patients with CKD present several complex management issues. The staging system introduced in 2002 by the National Kidney Foundation is a significant accomplishment, which stratifies patients according to disease severity. In addition, the K/DOQI guidelines are an excellent tool for management of CKD and dialysis patients and recommend treatments according to disease stage. These interventions may reduce morbidity and mortality in these patients. With early identification and treatment of anemia, renal osteodystrophy, uremic malnutrition, hyperlipidemia and cardiovascular disease, primary care physicians, and nephrologists together are making significant strides toward extending and improving the lives of patients with chronic renal disease.

CONCLUSION

Medication management in CKD offers unique challenges, but presents opportunities to enhance care quality to this high-risk population. Implementing strategies to evaluate the heavy medication burden of many patients with CKD, considering the risks and benefits of all prescribed agents, and deprescribing when indicated may improve patient outcomes. The implications of reduced kidney function in a disease population with a range of comorbidities are substantial, and recognizing these can have a significant effect on care management of patients with CKD and has the potential to reduce much of their morbidity and mortality.

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