Hyperkalemia Associated with Angiotensin Converting Enzyme Inhibitor or Angiotensin Receptor Blockers in Chronic Kidney Disease

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ABSTRAK

Inhibisi dari renin – angiotensin – aldosteron system (RAAS) merupakan strategi kunci untuk mengatasi hipertensi pada penyakit jantung dan ginjal. Namun, penghambat RAAS (penghambat enzim konversi angiotensin, penghambat reseptor angiotensin, penghambat reseptor aldosteron, dan penghambat renin) meningkatkan resiko hiperkalemia (kadar kalium serum > 5.5 mmol/L). Hal ini menimbulkan tantangan karena kelompok pasien dengan hiperkalemia ini membutuhkan terapi khusus. Pertimbangan untuk menginisiasi ACEI atau ARB dengan melihat estimasi laju filtrasi glomerulus, konsentrasi kalium basal dan melihat asupan kalium yang berlebihan, suplemen atau obat yang dapat meningkatkan kalium menjadi penting. Pemeriksaan kalium setelah inisiasi terapi dapat mencegah terjadinya hiperkalemia. Bila hiperkalemia terjadi, pengenalan terhadap disritmia kardiak dan terapi antagonis dari efek potassium terhadap jantung, meredistribusi kalium ke dalam sel, dan mengeluarkan kelebihan kalium perlu segera dilakukan. Pengetahuan dan kewaspadaan serta monitoring akan pemberian ACEI dan ARB terutama pada gagal ginjal kronis dapat meminimalisiasi kejadian hiperkalemia.

Kata kunci: hiperkalemia, penghambat enzim konversi angiotensin, penghambat reseptor angiotensin, gagal ginjal kronis.

ABSTRACT

Inhibition of the renin-angiotensin-aldosterone system (RAAS) is a key strategy in treating hypertension in cardiovascular and renal diseases. However, RAAS inhibitors (angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, aldosterone receptor antagonists, and direct renin inhibitors) increase the risk of hyperkalemia (serum potassium >5.5 mmol/L). This poses a therapeutic challenge because these patient groups comprise in whom the drugs are therapeutically indicated. Important considerations when initiating ACEI or ARB therapy include obtaining an estimate of glomerular filtration rate and a baseline serum potassium concentration, as well as assessing whether the patient has excessive potassium intake from diet, supplements, or drugs that can also increase serum potassium. Serum potassium monitoring shortly after initiation of therapy can assist in preventing hyperkalemia. If hyperkalemia does develop, prompt recognition of cardiac dysrhythmias and effective treatment to antagonize the cardiac effects of potassium, redistribute potassium into cells, and remove excess potassium from the body is important. Understanding the mechanism of action and monitoring of ACEI and ARB coupled with judicious drug use and clinical vigilance can minimize the risk to the patient of developing hyperkalemia.

Keywords: hyperkalemia, angiotensin converting enzyme inhibitor, angiotensin receptor blocker, chronic kidney disease.

INTRODUCTION

Angiotensin-converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB) are used to lower blood pressure, treat heart failure, decrease cardiovascular morbidity and death after myocardial infarction, blunt progression of renal disease in non diabetic patients with chronic kidney disease (CKD), and slow renal disease progression in patients with type 2 diabetes.[1] ACEIs and ARBs have shown efficacy in decreasing proteinuria, and slowing the progression of diabetic nephropathy. Their use, however, is sometimes complicated by hyperkalemia that may necessitate their discontinuation.[2]

The use of ACEI/ARB in patients with advanced renal disease may be complicated by hyperkalemia because of decreased urinary potassium excretion from impaired glomerular filtration and/or a decline in aldosterone levels. The extent of renal impairment, the coadministration of drugs inhibiting kaliuresis and/or diabetes may also modulate serum potassium excretion in these patients.[3]

Hyperkalemia occurs in up to 10% of hospitalized patients, with 10% of those patients (i.e., up to 1% of hospitalized patients) having serum potassium greater than or equal to 6 mmol/L.[4] ACEI/ARB therapy is considered a contributing cause in 10% to 38% of hospitalized hyperkalemia cases.[5] In ambulatory practice, ACEI/ARB therapy also contributes to hyperkalemia in up to 10% of patients[3,6] with about 1% of patients with diabetes experiencing serious hyperkalemia.[4] Furthermore, ACEI/ARB therapy is implicated in hyperkalemia in as many as 6% of patients enrolled in clinical trials.[7]

In Stockholm Creatinine Measurements (SCREAM) project with potassium monitoring in the year following ACE-I or ARB initiation (N=52 996) Potassium >5 mmol/L occurred in 5.6% (N=2977), potassium >5.5 mmol/L occurred in 1.7% (N=924), and potassium >6 mmol/L occurred in 0.63% (N=334). Hyperkalemia occurred much more frequently among people with lower eGFR. For example, among people with eGFR <30 mL/min per 1.73 m², new users of ACEI or ARB therapy had a 55% and 29% 1-year occurrence of potassium >5 and >5.5 mmol/L, respectively.[8]

Concern about the limit of hyperkalemia after initiation of ACEI or ARB become important but the guideline which monitoring of potassium still unclear. Hyperkalemia with use of ACEI or ARB in chronic kidney disease will futher discuss.

CLASSIFICATION

Hyperkalemia can be classified according to serum potassium into mild (5.5–6.5 mmol/l), moderate (6.5–7.5 mmol/ l) and severe (>7.5 mmol/l) hyperkalemia. Hyperkalemia not only rarely associated with symptoms, occasionally patients complain of palpitations, nausea, muscle pain, or paresthesia but also life threatening complications.[9]

CKD is defined as kidney damage or glomerular filtration rate (GFR) <60 mL/min/1.73 m² for 3 months or more, irrespective of cause. Kidney damage in many kidney diseases can be ascertained by the presence of albuminuria, defined as albumin-to-creatinine ratio >30 mg/g in two of three spot urine specimens. GFR can be estimated from calibrated serum creatinine and estimating equations, such as the Modification of Diet in Renal Disease (MDRD) Study equation or the Cockcroft-Gault formula 10. CKD could be classified according to severity, diagnosis, treatment and prognosis (**Table 1**).

PATHOPHYSIOLOGY

The renin – angiotensin - aldosterone system (RAAS) is a well known regulator of blood pressure (BP) and determinant of target organ damage. It controls fluid and electrolyte balance through coordinated effects on the heart, blood vessels, and Kidneys.[11]

ACE (also known as kininase II) is a relatively non-selective dipeptidyl carboxypeptidase that accepts various substrates, including angiotensin I and bradykinin. ACE catalyses the hydrolysis of bradykinin to inactive products and converts the inactive decapeptide angiotensin I to the biologically active octapeptide angiotensin II.[12] Angiotensin II is the main effector of the RAAS and exerts its vasoconstrictor effect predominantly on the postglomerular arterioles, thereby increasing the glomerular hydraulic

Table 1. Classification of chronic kidney disease

Stage	Description	Classification by severity		Classification by treatment
		GFR mL/min/1.73 m^2	Related terms	
1	Kidney damage with normal or ↑ GFR	≥ 90	Albuminuria, proteinuria, hematuria	
2	Kidney damage with mild ↓ GFR	60-89	Albuminuria, proteinuria, hematuria	
3	Moderate ↓ GFR	30-59	Chronic renal insufficiency, early renal insufficiency	T if kidney transplant recipient
4	Severe ↓ GFR	15-29	Chronic renal insufficiency, late renal insufficiency, pre-ESRD	
5	Kidney failure	< 15 (or dialysis)	Renal failure, uremia, end-stage renal disease	
				D if dialysis (hemodialysis, peritoneal dialysis)

pressure and the ultrafiltration of plasma proteins, effects that may contribute to the onset and progression of chronic renal damage.[11] Angiotensin II elevates blood pressure by various mechanisms, including direct vasoconstriction, potentiation of the activity of the sympathetic nervous system at both central and peripheral levels, stimulation of aldosterone synthesis and release with consequent sodium and fluid retention by the kidney, and stimulation of arginine vasopressin release.

Renin secretion is influenced by intra and extra renal factors such as low renal perfusion pressure, β-adrenergic stimulation, prostaglandins, angiotensin II, potassium, and sodium. Decreased sodium and chloride delivery to the distal tubule stimulate renin release. Renin acts on angiotensinogen in the blood to form angiotensin I, which is converted by angiotensin-converting enzyme (ACE) to angiotensin II. Angiotensin II stimulates the release of aldosterone from zona glomerulosa cells in the adrenal cortex. Aldosterone secretion is also influenced by plasma potassium. Angiotensin II and potassium act synergistically on aldosterone release.

Aldosterone directly affects kidney potassium handling. Potassium secretion in the collecting duct is regulated primarily by serum aldosterone concentrations and the amount of sodium delivered to the distal nephron. Aldosterone binds to a receptor in collecting duct cells and stimulates sodium reabsorption across the luminal membrane through a sodium channel. As sodium is reabsorbed, the lumen becomes more electronegative and provides a favorable environment for potassium secretion through a potassium channel.[7]

Drugs acting on the RAAS include agents that inhibit renin synthesis and release; that is, the direct renin inhibitors and β-adrenoceptor blockers, the ACE inhibitors, the ARBs, the aldosterone-receptor antagonists (ARAs) and a new class of combined ACE and neutral endopeptidase (NEP) inhibitors, called the vasopeptidase inhibitors (VPIs). A total of 17 ACE inhibitors have been developed for clinical use, and many have been approved for the treatment of hypertension, heart failure, diabetic nephropathy and/or left ventricular dysfunction. All ACE inhibitors act by binding to the active site of ACE and interfering with the ability of the enzyme to bind to and cleave its substrates, angiotensin I and bradykinin.

These compounds proved to be highly successful in the treatment of hypertension and related target-organ damage, including left ventricular hypertrophy, heart failure and post myocardial infarction left ventricular remodelling renal insufficiency and diabetes with proteinuria.

The ARBs are non-peptide compounds that specifically block the binding of angiotensin II to the AT1 receptor by occupying the space among

the seven transmembrane helices of the receptor protein, and interacting with the amino-acid residues in this region of the receptor molecule. They do not interact with AT2 receptors. ARB administration indirectly activates the AT2 receptor by blocking feedback inhibition of renin release and thereby activating the RAAS cascade and causing more angiotensin II to be generated, and shunting the angiotensin II so generated from AT1 to AT2 receptors.[12]

Under normal circumstances, there is an inverse relationship between the plasma aldosterone concentration and the delivery of sodium to the distal nephron so that potassium excretion remains independent of changes in extracellular fluid volume. Under conditions of decreased renal perfusion, aldosterone concentrations increase. At the same time, the proximal absorption of sodium and water increases, and as a result, their distal delivery decreases. Renal potassium excretion remains fairly constant under these conditions, since the stimulatory effect of increased aldosterone is counterbalanced by the decreased delivery of filtrate to the distal nephron.

Mild to moderate reductions in renal perfusion typically do not cause the distal delivery of sodium to fall to a level that impairs potassium secretion sufficiently to result in clinically significant hyperkalemia. In most patients with untreated congestive heart failure, the serum potassium concentration is normal or at the high end of the normal range as long as the impairment in cardiac function and renal perfusion is not severe. When such patients are treated with ACE inhibitors or angiotensin-receptor blockers, the fall in the circulating aldosterone concentration typically will be counterbalanced by increased distal delivery of sodium so that the serum potassium concentration remains stable. The increase in the distal delivery of sodium is due to the afterload-reducing effects of these drugs, which cause an improvement in cardiac output and renal perfusion. The reduction in angiotensin II concentration plays an important role in decreasing proximal sodium reabsorption. In addition, most patients are treated with loop diuretics, which further enhance the delivery of sodium to the collecting duct.

When renal perfusion becomes more severely reduced, as in intractable congestive heart failure, proximal reabsorption can become so intense that very little sodium escapes into the distal nephron. Despite increased concentrations of aldosterone, the lack of availability of sodium can begin to impair renal potassium secretion. To the extent that cardiac output and renal perfusion become refractory to the afterload-reducing effects of ACE inhibitors or angiotensin-receptor blockers, the risk of hyperkalemia increases. In this setting, these drugs may also cause the serum creatinine concentration to rise owing to reductions in intraglomerular pressure that are no longer offset by increases in glomerular perfusion.[7]

MANAGEMENT

The risk of severe complications and the urgency for treatment of hyperkalemia is determined by individual patient conditions including presenting symptoms, overall hemodynamic status, kidney function, underlying medical conditions, patient medications, rapidity of potassium rise, serum potassium level, acid-base status, ECG findings, and so on.[13]

The initial approach to such a patient is to determine the specific risk of hyperkalemia by accurately assessing the level of renal function (**Table 2**).[7]

In patients with chronic kidney disease, the level of renal function should not be the sole criterion for deciding whether use of these drugs should be initiated or continued. When they are used in patients with severe reductions in the glomerular filtration rate (i.e., those with rates below 30 ml per minute), close monitoring is required. Withholding these drugs solely on the basis of the level of renal function will unnecessarily deprive many patients of the cardiovascular benefit that they otherwise would have received, particularly since numerous steps can be taken to minimize the risk of hyperkalemia.

Patients should follow a low-potassium diet with specific counseling against the use of salt substitutes that contain potassium. Diuretics are particularly effective in minimizing hyperkalemia. Diuretics enhance the excretion of potassium in the kidney by increasing the delivery of sodium to the collecting duct. In patients with an estimated

Table 2. Approach to patients at risk for hyperkalemia caused by inhibitors of the renin–angiotensin–aldosterone system.

Estimate glomerular filtration rate to assess specific risk of hyperkalemia

Whenever possible, discontinue drugs that interfere in renal potassium secretion, inquire about use of herbal preparations, and discontinue non- steroidal antiinflammatory drugs, including selective cyclooxygenase-2 inhibitors

Prescribe low-potassium diet; inquire about use of salt substitutes that contain potassium

Prescribe thiazide or loop diuretics (loop diuretics necessary when estimated glomerular filtration rate is <30 ml/min)

Prescribe sodium bicarbonate to correct metabolic acidosis in patients with chronic kidney disease: 1 or 2 650-mg tablets twice a day (each tablet contains 8 mEq of sodium bicarbonate) or 1/2–1 tsp of baking soda daily (25–50 mEq of sodium bicarbonate)

Initiate therapy with low-dose ACE inhibitor or angiotensin-receptor blocker

Measure potassium 1 week after initiating therapy or after increasing dose of drug

If potassium increases to ≤5.5 mmol/liter, decrease dose of drug; if patient is taking some combination of an ACE inhibitor, an angiotensin-receptor blocker, and an aldosterone-receptor blocker, discontinue one and re- check potassium

The dose of spironolactone should not exceed 25 mg daily when used with an ACE inhibitor or angiotensin-receptor blocker; this combination of drugs should be avoided when the glomerular filtration rate is <30 ml/min

If potassium is >5.5 mmol/liter despite steps described above, discontinue drugs

glomerular filtration rate that is 30 ml per minute or higher, thiazide diuretics can be used, but in patients with more severe renal insufficiency, loop diuretics are required.[7]

In patients with chronic kidney disease and metabolic acidosis, the administration of sodium bicarbonate is an effective strategy to minimize increases in the serum potassium concentration.[14] If treatment with an ACE inhibitor or an angiotensin-receptor blocker is to be initiated, it is best to begin with low doses. The serum potassium concentration should be checked within one week after the drug has been started. If the potassium con- centration is normal, then the dose of the drug can be titrated upward. With each increase in the dose, the serum potassium concentration should be measured again one week later.[15]

If the serum potassium concentration is 5.6 mmol per liter or higher despite the precautions described above, then such drugs may need to be avoided. Particular attention should be given to patients with underlying disturbances of cardiac conduction, since even mild degrees of hyperkalemia can precipitate heart block.[7]

However, typical electrocardiography (ECG) changes in a patient with hyperkalemia, increases the urgency for treatment. The ''classic'' ECG changes associated with hyperkalemia are well described. The earliest changes, often beginning with levels above 6.5 mEq/L, are ''peaked,'' or ''tented'' T-waves, which are most prominent in the precordial leads. With further rise in serum levels, there is diminished cardiac excitability manifested by flattening of the P-wave, PR interval lengthening, and the eventual disappearance of the P- wave. The QRS duration becomes prolonged, progressing to a ''sine wave'' appearance, and finally ending in ventricular asystole or fibrillation with levels 8 to 10 mmol/L.[13]

CONCLUSION

ACEI and ARB are effective therapeutic agents but can cause mild to life threatening hyperkalemia particularly in chronic kidney disease. To minimize the risk of hyperkalemia in patients initiate ACEI or ARB, filtration glomerular rate and serum potassium level must be estimated, drug that interfere in renal potassium secretion, potassium intake, supplements should be evaluated. If hyperkalemia occur, definitive treatment such as prevention of cardiac dysrhythmia and remove excess of potassium from the body can optimize the outcome.

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