

Managing Hyperkalaemia In Heart Failure Patients- A Review Of A Case Study At The Komfo Anokye Teaching Hospital, Kumasi, Ghana.

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Citation

C ANANE. *Managing Hyperkalaemia In Heart Failure Patients- A Review Of A Case Study At The Komfo Anokye Teaching Hospital, Kumasi, Ghana.*. The Internet Journal of Cardiology. 2009 Volume 9 Number 2.

Abstract

PURPOSE: Angiotensin-converting-enzyme (ACE) inhibitors, Angiotensin-receptor blockers (ARBs), Aldosterone-antagonists and recently Beta-adrenergic blockers are all neurohormonal blocking agents of the renin-angiotensin-aldosterone system. These drugs are used in clinical practice to treat heart failure. A side effect of such therapy is the development of hyperkalaemia. Determination of the incidence of clinical important hyperkalaemia in heart failure patients treated with the above recommended therapy forms the basis of this overview. **SETTING:** The Medicine Directorate of Komfo Anokye Teaching Hospital, KATH, Kumasi, Ghana, West Africa. KATH is located in Kumasi, the capital of Ashanti Region in Ghana. The geographical location of the 1000-bed teaching hospital, the road network of the country and commercial nature of Kumasi make the hospital accessible to all areas that share boundaries with the Region. The Directorate of Medicine has 220 beds and the patients admitted at the wards aged from 13 years and above. The directorate runs emergency service 24 hours, seven days a week. Referrals from regional hospitals, district hospitals, general practitioners and private clinics are admitted to the medical wards through the emergency unit. A case study involving a 32-year old female who presented with breathlessness, dizziness and easy fatigability for 2-day duration was admitted at the medical ward of KATH. A full blood count revealed the following; Sodium 145mmol/L (normal range 135-145mmole/l) and Serum Potassium 6.5mmole/l (normal range 3.5-5.4mmole/l). The woman was diagnosed as having heart failure NYHA IV, fast Atrial Fibrillation, with severe rheumatic mitral regurgitation and mitral stenosis. The high serum potassium was described as moderate hyperkalaemia. **Conclusion:** Heart failure patients undergoing treatment must have their full blood count investigated before initiation of therapy and two weeks after to monitor levels of electrolytes. High serum sodium will cause fluid retention and aggravate generalized oedema. Potassium level >5.5mmol/l is likely to cause significant hyperkalaemia. Patients' medical history must be reviewed and appropriate treatment given.

INTRODUCTION

Heart failure is a clinical syndrome characterized by the functional inability of the ventricle to provide adequate perfusion to meet the metabolic demands of the body resulting in symptoms of congestion or hypoperfusion. As a result, the renin-angiotensin-aldosterone system is activated to compensate for the hypoperfusion. However, this contributes to the pathology of the disease by among other actions, increasing the release of angiotensin II and aldosterone. Aldosterone has been shown to cause coronary inflammation, cardiac hypertrophy, myocardial fibrosis, ventricular arrhythmias, ischaemic and necrotic lesions. Angiotensin II causes direct vasoconstriction, stimulates catecholamine release from the adrenal medulla, and increases centrally mediated sympathetic nervous system activity.

Aldosterone promotes sodium and water retention by inducing the synthesis of the proteins that constitute the Sodium, Potassium-ATPase pump in the cortical collecting ducts. The results are sodium and water retention and potassium secretion. This neurohormonal response to renal hypoperfusion increases ventricular preload, myocardial contractility and heart rate[1]. Initially, the results are improved perfusion and a delay in heart failure symptoms. However, the compensatory mechanisms that delay these symptoms result in myocardial remodeling. The modeling worsens ventricular function, perpetuating hypoperfusion. The result is an angiotensin II-induced hyperadrenergic, hyperaldosterone state that eventually leads to clinical heart failure.

The neurohormonal pathology of heart failure is a significant

contribution of the progressive morbidity and mortality associated with the disease[1]. The pharmacotherapy of heart failure depends on the neurohormonal blockade of these pathways with angiotensin-converting-enzyme Inhibitors, angiotensin-receptor blockers, aldosterone-antagonists and beta-adrenergic blockers. Hyperkalaemia develops in approximately 10 to 38% of hospitalized heart failure patients put on these drugs. Heart failure patients at greatest risk for hyperkalaemia include those with diabetes and those with impaired renal function in whom a defect in the excretion of renal potassium may already exist.

Hyperkalaemia, technically, means an abnormally elevated level of potassium in the blood. The normal potassium level in the blood is 3.5-5.0milliequivalents per litre (mEq/L). Potassium levels between 5.1mEq/L to 6.0mEq/L are moderate hyperkalaemia and levels above 7mEq/L are severe hyperkalaemia[2].

Potassium is critical for the normal functioning of the muscles, heart and nerves. It plays an important role in controlling activity of smooth muscle such as the muscle found in the digestive tract and skeletal muscle such as muscles of the extremities and torso as well as the muscles of the heart. It is also important for the nervous system within the body.

The most important clinical effect of hyperkalaemia is related to electrical rhythm of the heart. Whole mild hyperkalaemia probably has a limited effect on the heart, moderate hyperkalaemia can produce electrocardiography (ECG) changes and severe hyperkalaemia can cause suppression of electrical activity of the heart leading to cardiac arrest and death.

INDUCTION OF HYPERKALAEMIA

Angiotensin-converting-enzyme (ACE) inhibitors and Angiotensin-receptor-blockers (ARBs) impair urinary potassium excretion by interfering with the stimulatory effect of angiotensin II on aldosterone secretion in the adrenal gland. ACE inhibitors block the formation of angiotensin II, whereas ARBs prevent angiotensin II from binding to its adrenal receptor. Hyperkalaemia may develop as a complication of therapy with ACE inhibitors or ARBs in patients with one or more of three disturbances that impair the excretion of potassium i.e. decreased delivery of sodium to the distal nephron; aldosterone deficiency; and abnormal functioning of the cortical collecting tubule. These abnormalities can result from the effects of other drugs, from

underlying disease, or commonly from a combination of both.

Several major randomized controlled trials have shown, conclusively that certain beta-blockers increase survival, reduce hospital admissions and improve NYHA class and quality of life when added to standard therapy in patients with stable mild and moderate heart failure and in some patients with severe heart failure. In spite of their usefulness heart failure therapy, beta-blockers can confer a predisposition to the development of hyperkalaemia through two potential mechanisms. These drugs block the stimulatory effect of the sympathetic nervous system on the release of renin. In addition, they can interfere with the cellular uptake of potassium through decreased activity of sodium, potassium-ATPase pump[3]

Aldosterone acts in the renal cortical collecting ducts by inducing synthesis of proteins that constitute the sodium, potassium-ATPase pump. The pump acts to re-absorb sodium and water in exchange for potassium, which is then eliminated in the urine. Consequently, aldosterone antagonism causes hyperkalaemia. Hyperkalaemia is an established adverse effect of spironolactone. The major clinical trials of aldosterone antagonists in heart failure have found dosage-related elevations in serum potassium values[1].

EPIDEMIOLOGY

In the United States, the incidence of hyperkalaemia ranges from 1-10% depending on the definition of hyperkalaemia. As in the U.S, the incidence of hyperkalaemia in the general population has been reported in less than 5% of people. Patients who are hospitalized in countries as diverse as England, Australia and Israel experience hyperkalaemia approximately 10% of the time[4]

Schepkens[5] and colleagues reported an analysis of 25 cases of severe hyperkalaemia with mean potassium level of 7.7mmole/L that occurred during combined therapy with an ACE inhibitor and spironolactone, the average baseline creatinine level in these patients was 168µmol/L.

Obiolo[6] and colleagues described 18 cases of hyperkalaemia in elderly patients with heart failure receiving spironolactone who had renal insufficiency with estimated GFR<60ml/min but normal creatinine levels.

Wrenger[7] and colleagues reported a case series of 44 patients with heart failure admitted for hyperkalaemia who

were taking spironolactone plus an ACE inhibitor or ARB. The average serum potassium concentration on admission was 7.7mmol/L. 80% of these pats (n=35) had diabetes. 34 had a baseline creatinine clearance of ≤ 30 ml/min.

Cruz [8] and colleagues retrospectively reviewed patients admitted for decompensated heart and treated with an ACE inhibitor with or without spironolactone. Of the 49 patients taking both agents, 16 developed hyperkalaemia with potassium level >5.5 mEq/mL, 7 cases of which were severe with potassium level $>$

6.0mEq/ml. All 7 patients with severe hyperkalaemia had NYHA class heart failure.

Svensson et al[9] identified 125 consecutive patients in a heart failure clinic, 86% of whom were taking an ACE inhibitor or ARB. Spironolactone was added or continued in each patient. Logistic regression was performed for baseline serum creatinine concentrations, age, sex, left ventricular ejection fraction, and use of ACE inhibitors or β -adrenergic blockers but not for ACE inhibitor dosage. 10% of the study patients developed severe hyperkalaemia with potassium levels > 6.0 mEq/ml.

No racial predisposition to hyperkalaemia appears to exist but men are significantly more prone to hyperkalaemia than women. This difference has been noted in several series and stands in contrast to the increased incidence of hypokalaemia in women. The reasons for this discrepancy are unknown.

Several series document the increasing tendency for hyperkalaemia in patients at the extremes of life, either small premature infants or elderly people, with renal insufficiency playing a significant role in both.

AETIOLOGY

The major causes of hyperkalaemia are kidney dysfunction, diseases of the adrenal gland, potassium shifting out of cells into the blood circulation and medications as discussed above.

Potassium is normally excreted by the kidneys, so disorders that decrease the function of the kidneys can result in hyperkalaemia. These include acute and chronic renal failure, glomerulonephritis, lupus nephritis, transplant rejection and obstructive diseases of the urinary tract such as urolithiasis.

Adrenal glands are important in secreting hormones such as

cortisol and aldosterone. Aldosterone causes the kidneys to retain sodium and fluid while excreting potassium in the urine. Therefore, diseases of the adrenal gland, such as Addison's disease that lead to decreased aldosterone secretion can decrease kidney excretion of potassium, resulting in body retention of potassium, and hence hyperkalaemia.

Shift from intracellular to extracellular space alone is a relatively uncommon cause of hyperkalaemia but can exacerbate hyperkalaemia produced by a high intake or impaired renal excretion. Clinical situations in which this mechanism is the major cause of hyperkalaemia include hyperosmolality, rhabdomyolysis, tumour lysis and succinyl choline administration, which depolarizes the cell membrane and, thus, permits potassium to leave the cells. However, more often, mild to moderate impairment of intracellular shifting of potassium occurs with insulin deficiency or acute acidosis.

MORTALITY/MORBIDITY

When not recognized and treated properly, severe hyperkalaemia results in a mortality rate of about 67%[4]. Hyperkalaemia in a heart failure patient who is hospitalized is an independent risk factor for death. In one series, 1.4% of heart failure patients who were hospitalized (406 out of 29,063) developed hyperkalaemia. The overall mortality rate in patients with hyperkalaemia was 14.3% (58 out of 406 patients) with the risk increasing as potassium increases. 28% of patients with a serum potassium level greater than 7mEq/L died, as opposed to 9% of those with a potassium level less than 6.5mEq/L. In 7 out of 58 deaths, cause of death was directly attributable to hyperkalaemia. Most cases resulting in death were complicated by renal failure. Paice B et al reported that all patients who died of hyperkalaemia had normal potassium levels within 36 hours prior to death[9].

SIGNS AND SYMPTOMS

Symptoms are non-specific and predominantly related to muscular or cardiac function. The most common complaints are weakness and fatigue. Occasionally a patient may complain of frank muscle paralysis or shortness of breath. Patients also may complain of palpitations or chest pain.

As serum potassium level rise symptoms progress to more significant muscle twitching, weakness, nausea, cramping and flaccid paralysis.

DIAGNOSIS

In general, the results of physical examination alone do not alert the clinician to the diagnosis except when severe bradycardia is present or muscle tenderness accompanies muscle weakness, suggesting rhabdomyolysis[4].

Physical examination includes general assessment to look for tachypnea due to respiratory muscle weakness, flaccid paralysis and depressed or absent deep tendon reflexes.

Routine blood tests to check for anaemia due to volume depletion, blood sugar, kidney liver and thyroid function tests are investigated to aid diagnosis.

Full blood count to note plasma level of potassium and serum creatinine will aid diagnosis. Electrocardiograph (ECG) is done to confirm the diagnosis of hyperkalaemia. ECG changes include tall “tenting” T waves; small or absent P wave with increased P-R interval and widened QRS complex. Cardiac conduction abnormalities can begin with peaked T waves at serum potassium concentrations of 5.5-6.0mEq/L. As serum potassium values increase, the P-R and QRS intervals become prolonged and conduction abnormalities become more severe, eventually resulting in life-threatening ventricular fibrillation or asystole.

MANAGEMENT OF HYPERKALAEMIA

The risk of hyperkalaemia increases when ACE inhibitors and Angiotensin-receptor blockers are used with aldosterone-antagonist, spironolactone in the treatment of heart failure in the presence of other commodity or diseases that interfere with the function of the cortical collecting tubule as in renal insufficiency or in diabetes mellitus.

The initial approach to such patients is to determine the specific risk of hyperkalaemia by accurately assessing the level of renal function[10]. In general, the risk will increase as renal function declines. However, an estimated glomerular filtration rate of 30ml per min should be considered a threshold below which the likelihood that hyperkalaemia will develop substantially increases. Heart failure patients with diabetic nephropathy who have only mild-to-moderate reductions in the glomerular filtration rate (30-90ml per min) should be considered at higher risk because of the frequent presence of hyporeninemic hypoaldosteronism.

In heart failure patient 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 heart failure patients with severe reductions in the glomerular filtration rate i.e. those with rates below 30ml per min, 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 hyperkalaemia. If treatment with an ACE inhibitor or an ARB is to be initiated, it is best to begin with low doses. The serum potassium concentration should be checked within one week after initiation of therapy. If the potassium concentration 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. For increased serum potassium concentrations up to 5.5mEq/L, the dose can be lowered. In some cases, the potassium concentration will decline and treatment with the Renin-angiotensin blockers can be continued albeit at lower dose. In patients receiving the combination of an ACE inhibitor, an ARB and aldosterone antagonist, spironolactone discontinuation of one drug may also be effective in lowering the serum potassium concentration. If potassium concentration is 5.6mEq/L or higher despite the precautions described above, 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 hyperkalaemia can precipitate heart block.

APPROACH TO PATIENTS AT RISK FOR HYPERKALAEMIA CAUSED BY INHIBITORS OF THE RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM

- Estimate glomerular filtration rate or Creatinine clearance to assess specific risk of hyperkalaemia using the formula

TREATMENT OF HYPERKALAEMIA

Treatment of hyperkalaemia must be individualized based upon the underlying cause of the hyperkalaemia, the severity of symptoms or appearance of ECG changes and the overall health status of the patient.

Treatment of hyperkalaemia may include any of the following measures either singly or in combination;

- The patient should follow a low-potassium diet (

for mild cases)

- In the heart failure patient is on all the neurohormonal blocking agents consider discontinuing one or two of these medications
- Intravenous administration of 50ml of 50% dextrose and 20 units of soluble insulin, which promotes movement of potassium from the extracellular space back into the cells.
- Nebulized salbutamol (2-5mg) also makes potassium enter cells from extracellular spaces
- Intravenous calcium to temporarily protect the heart and muscles from the effects of hyperkalaemia
- Sodium bicarbonate administration to counter acidosis and to promote movement of potassium from the extracellular space back into the cells.
- Medications that stimulate beta-2-adrenergic receptors such as albuterol and epinephrine have also been used to drive potassium back into cells.
- Diuretics are particular effective in minimizing hyperkalaemia. Diuretics enhance the excretion of potassium in the kidney by increasing the delivery of sodium to the collecting duct. In patients with an estimated glomerular filtration rate that is 30ml per min or higher, thiazide diuretics can be used but in patients with more severe renal insufficiency, loop diuretics are required.

MONITORING/COUNSELLING

Heart failure patients undergoing treatment must have their full blood count investigated before initiation of therapy and two weeks after to monitor levels of electrolytes. High serum sodium will cause fluid retention and aggravate generalized oedema. Potassium level $>5.5\text{mmol/l}$ is likely to cause significant hyperkalaemia. Patients' medical history must be reviewed. Patients should be asked specifically about the use of over-the-counter-non-steroidal anti-inflammatory drugs (NSAIDs). NSAIDs have been reported to cause hyperkalaemia in up to 46% of hospitalized patients[11]. These drugs interfere with the stimulatory effect of prostaglandins on the release of renin[12] The subsequent fall in aldosterone concentrations is exacerbated when these drugs are used with inhibitors of the renin-angiotensin-aldosterone system, since prostaglandins serve an

intermediary role in the stimulatory effect of Angiotensin II on aldosterone secretion[13] The cyclooxygenase-2-selective inhibitors should be used with the same caution that applies to the use of traditional NSAIDs[14]

Heart failure patients in addition to taking the standard heart failure therapy are sometimes put on heparin—fractionated or unfractionated. These drugs block the biosynthesis of aldosterone in the adrenal gland. This complication can develop irrespective of the dose used and may be seen after either intravenous or subcutaneous administration[15]

Heart failure patients on treatment must be counseled on the use of theazole antifungals such as ketoconazole, which interferes with the biosynthesis of adrenal steroids and therefore can predispose patients to aldosterone deficiency.

Concomitant use of trimethoprim-sulphamethoxazole which can interfere with the excretion of potassium should be avoided.

It is important to inquire about the use of herbal medications by heart failure patient on standard treatment since herbs may be a hidden source of dietary potassium. An example of such herbal preparation is noni juice, which derived from the fruit of the noni tree (*Morinda citrifolia*) and contains 56mmole of potassium per litre[16]. Substantial quantities of potassium are also found in alfalfa (*Medicago sativa*) and nettle (*Urtica dioica*)[17]

Patients should follow a low-potassium diet with specific counselling on the use of salt substitutes that contain potassium[18]. Foods rich in potassium include orange juice, melons and bananas.

CASE REPORT

A 32-year-old female patient, H.A. was admitted at the medical ward on 10th March, 2008.

HA presented with breathlessness at rest which was associated with dizziness and easy fatigability upon slight exertion. On direct questioning, HA had orthopnoea, paroxysmal nocturnal dyspnoea, and palpitations. Her medical history consists of the following medication; isosorbide dinitrate 10mg tds, warfarin 5mg nocte, lisinopril 5mg daily, aldactone 25mg daily and aspirin 300mg.

The family history was that only the brother is hypertensive. There was no known history of sudden death, diabetes, and sickle cell disease.

HA is currently unemployed married with three children, non-alcoholic and non-smoker.

On examination, it was found that HA was dyspnoec, tachymic, afebrile with a temperature of 36.3°C, moderately palour and anicteric.

On central nervous system examination, her jugular vein pressure (JVP) was raised with apex beat at the left 6th intercostal space. Her pulse rate was 136beats/min and was irregularly irregular with weak volume.

There were SI, SII and SIII sounds with gallop rhythm. Her B.P on admission was 110/90mg/Hg and had a respiratory rate of 38cycles/min with a chest X-ray showing Cardiomegaly (CTR=0.75).

The Electrocardiography (ECG) shown the following; heart rate was 161beats/min with right axis deviation. The rhythm was found to be atrial fibrillation, right bundle block (incomplete) with right ventricular hypertrophy.

Her laboratory results shown the following; Full blood count; WBC 4.87, RBC 4.65, HB 11.5; electrolytes sodium 145mmole/l, potassium 6.5mmole/l (normal range 3.5-5.4mmole/l), creatinine(SI) 106.1mmole/l, urea 3.3mmole/l

IMPRESSION OF THE CARDIOLOGY TEAM

Impression was made as follows; HA was diagnosed as having Heart failure NYHA class IV, with the following differentials fast Atrial fibrillation, severe rheumatic mitral regurgitation and mitral stenosis, moderate tricuspid regurgitation/pulmonary regurgitation, dilated left and right Atria, pulmonary hypertension, and moderate hyperkalaemia.

Figure 1

TABLE 1. THE PHARMACEUTICAL CARE PLAN

DATE	DRUGS	GOAL OF THERAPY
10/03/08	IV Lasix 120mgtds x 7	Diuresis
"	Tb Lisinopril 2.5mg dly x7	Decrease afterload
"	Tb Aldactone 25mg bd x3	Diuresis
"	Tb ISDN 10mg bd×14	Decrease preload
"	Tb Digoxin 0.25mg bd	Decrease heart rate
"	Tb Amiodiarone 200mg tds ×7	To change fibrillation to sinus rhythm

Figure 2

TABLE 2. RENAL FUNCTION TEST

TEST NAME	RESULTS	UNIT	RANGE
CREATININE	1.2	Mg/dL	(0.6-1.4)
CREATININE(SI)	106.1	umol/L	(53-124)
BUN/Crt	8.6	RATIO	(8.0-36)

Figure 3

TABLE 3. ELECTROLYTES

TEST NAME	RESULTS	UNIT	RANGE
Na 2+	145	mmol/L	(134-149)
K +	6.5	mmol/L	(3.6-5.5)
Cl -	94	mmol/L	(94-112)

Figure 4

TABLE 4. HAEMATOLOGY RESULT

TEST	RESULT	UNIT	REF. RANGE
WBC	4.87	k/ul	(2.5-10.0)
LYM	14.5	%L	(20.0-50.0)
RBC	4.65	m/uL	(4.2-6.30)
HGB	11.5	g/dL	(11.1-18.0)
HCT	41.6	%	(33.3-51.0)
MCV	79.0	fL	(80.0-97.0)

Figure 5

TABLE 5. PHARMACEUTICAL CARE ISSUES

DATE	CARE ISSUE	INTERVENTION	OUTCOME
10/03/09	Tb Aldactone 25mg bd x 3	Aldactone is potassium-sparing diuretic. Serum potassium is already high. Withdraw aldactone	Aldactone discontinued

MONITORING

MONITORING OF ELECTROLYTES

- K⁺ should be monitored
- Urine output
- B P
- Body weight
- Signs and Symptoms

HA was reviewed on 17th March, 2008 and discharged on the 18th March, 2008 to attend the cardiac clinic.

DISCUSSION

HA was diagnosed as having heart failure as a result of the signs and symptoms she presented and was confirmed by the laboratory and ECG results. HA had developed hyperkalaemia as a result of her medications before admission. The activation of the renin-angiotensin-aldosterone system due to her renal hypoperfusion had led HA being in a state of hyperadrenergic and hyperaldosterone state. Her medications were to mitigate the effects of this state. The result is the inhibition of the excretion of potassium at the distal collecting tubule. This led to a high serum potassium level. Diuretics are particularly effective in minimizing hyperkalaemia. Diuretics enhance the excretion of potassium in the kidney by increasing the delivery of sodium to the collecting duct. The loop diuretic, furosemide was able to correct the hyperkalaemia and also withdrawing aldactone was appropriate since aldactone is a potassium-sparing diuretic. On the 17th March, 2008, the serum potassium had dropped to 4.5mmol/l which was within the normal range. The blood pressure was 120/80mmHg and the pulse was 83 beats/min. and the patient was discharged on the following medications; tab Penicillin V 250mg bd x10, Soluble aspirin 75mg daily x30, tab Amiodarone 200mg bd x7, tab lasix 40mg daily x30, tab lisinopril 2.5mg daily x30. The patient was referred to the cardiac clinic.

COUNSELING

The patient was counseled on the following

- Reduce dietary salt intake
- Avoid strenuous work
- Moderate exercise and rest

- Compliance with drugs prescribed
- Regular BP check up
- Avoid over-the-counter NSAIDs

CONCLUSION

With the current knowledge in the management of Heart Failure, it is possible to tackle the problem of hyperkalaemia associated with the pharmacotherapy of heart failure and, therefore, it becomes imperative to always monitor the serum potassium levels before the commencement of therapy and two weeks after initiation. Believe me; Pharmacists have a role to play in this!

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