Pseudohyperkalaemia: Case Series and Review of Literature

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ABSTRACT

Pseudohyperkalaemia is a phenomenon characterized by spurious elevation of measured serum potassium concentration without the patient having increased circulating potassium levels in the blood. It is a fairly common laboratory artifact than can cause misleading diagnosis and inappropriate treatment of hyperkalaemia. To highlight the likelihood of occurrence of pseudohyperkalaemia and hence the need for its exclusion as a potential cause of laboratory error in the measurement of serum potassium concentration. We report four suspected, investigated, and established cases of pseudohyperkalaemia due to: (1) use of wrong specimen bottles, (2) improper specimen preservation, (3) in vitro sample haemolysis. In the four cases, measured plasma potassium concentrations were markedly higher than the critical value for plasma potassium concentration. However, repeat testing in each case revealed potassium levels within reference limits (3.5 5.1mmol/L) thereby confirming the diagnosis of pseudohyperkalaemia. Pseudohyperkalaemia is a fairly common phenomenon in contemporary clinical practice. Its occurrence must be excluded before a definitive diagnosis of (true) hyperkalaemia is made.

Keywords: Serum electrolytes, potassium, hyperkalaemia, pseudohyperkalaemia

INTRODUCTION

Measurement of serum electrolytes is a significant element of the day-to-day workload of most chemical pathology laboratories[1]. Serum potassium concentration is one of the components of the routine serum electrolytes profile. Generally, determination of serum electrolytes concentration helps in the assessment of hydration status, osmotic status, acid-base status, and renal function status[1]. Serum potassium measurement in particular, is necessary for the evaluation of renal function and acid-base status. In addition, plasma potassium concentration within the normal reference limits of 3.5mmol/L to 5.1mmol/L is necessary for the maintenance of resting membrane potential of all body cells and more especially the excitable cells such as the cardiac muscle cells[2]. Thus, both hypokalaemia (plasma potassium <3.5mmol/L) and hyperkalaemia (plasma potassium >5.1mmol/L) are potential causes of abnormal electrocardiogram (ECG) pattern, cardiac arrythmias, and eventually, cardiac arrest (when severe)[2].

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In the laboratory measurement of serum potassium concentration, several preanalytical factors have the potential to adversely influence the final test result. Notable among these factors are those that can cause spurious elevation of measured serum potassium concentration without the patient actually having increased circulating potassium levels in the blood (true hyperkalaemia). This condition is referred to as spurious hyperkalaemia, artifactual hyperkalaemia, factitious hyperkalaemia or pseudohyperkalaemia[3-6]. Pseudohyperkalaemia is a fairly common laboratory artifact that can be misleading to both clinical laboratorians and physicians. It has the potential to cause misdiagnosis and inappropriate treatment with attendant danger to the patient if unrecognized[5,6].

The likelihood of occurrence of pseudohyperkalaemia during the preanalytical phase of serum eletrolytes measurement, calls for its exclusion in any sample with measured high potassium concentration[7]. This becomes a necessity in situations where the patient does not have evident aetiological factors and clinical features associated with true hyperkalaemia. We reviewed cases of pseudohyperkalaemia established in four different specimens submitted for serum electrolytes analyses in a tertiary clinical laboratory in Calabar, Nigeria.

METHOD

We report four suspected, investigated, and established cases of pseudohyperkalaemia

due to: (1) use of wrong specimen bottles, (2) improper specimen preservation, (3) *in vitro* sample haemolysis. The serum potassium concentration in all cases was measured as a component of routine electrolytes profile using the ion selective electrode (ISE) assay method.

The serum electrolytes (including potassium) assay was performed by a dry ISE module of selectra Pro S autoanalyzer manufactured by ELI Tech Group B.V (Van Rensselaerweg 4 6956 AV Spankeren, the Netherlands). The autoanalyzer was daily calibrated and each assay run involved the measurement of levels 1 and 2 quality control sera to ensure analytical quality control.

CASE REVIEWS

Case 1 (Table 1): The patient is a 58-year old woman who is a known hypertensive. She visited a private specialist clinic where a venous blood specimen was collected for serum electrolytes analyses. The specimen was collected and submitted to laboratory by the managing physician. Following the analysis of the sample, the serum potassium result was 7.56mmol/L. The levels 1 and 2 control specimens that were run with the sample both gave serum potassium values within control limits. Based on the fact that the serum potassium level was repeatedly above 6.2mmol/L (the laboratory's critical value), the consultant chemical pathologist was immediately notified. Consequently, a call was put through to the requesting physician to notify him on the abnormally high serum potassium result that remained so even on several repeat testing. The requesting physician volunteered the information that the submitted blood specimen was collected with an ethylenediaminetetraacetic acid (EDTA) bottle that was "thoroughly washed and rinsed" with methylated spirit before it was used to collect the patients blood specimen.

Case 2 (Table 2): A whole blood specimen was collected into lithium heparin bottle from a 57 year old man for routine serum electrolytes, urea and creatinine analyses. Due to power outage, the sample could not be processed. Consequently the specimen was kept in the refrigerator compartment of the fridge over the night. The following morning, the sample was submitted to the laboratory for serum electrolytes, urea and creatinine analyses. The heparinized whole blood specimen was centrifuged and the supernatant plasma was harvested. The separated plasma sample under visual inspection did not show evidence of *in vitro* sample haemolysis. After sample analysis, the plasma potassium concentration was 11.6mmol/L which is higher than the upper critical value of 6.2mmol/L. Repeat testing yielded results that are consistently above 6.2mmol/L. Accordingly, the consultant chemical pathologist was notified. Investigations on the possible cause of this elevated serum potassium concentration for a patient on routine health check revealed the overnight preservation of the collected blood specimen in the refrigerator before submission to the laboratory.

Case 3 (Table 3): A plasma sample obtained from a 40- year old man was submitted to the laboratory for electrolytes, urea and creatinine analyses. The collected venous blood specimen was processed outside the laboratory (prior to submission) and the investigations were parts of a pre-surgical evaluation for an elective general surgery procedure. On sample analysis, the potassium result was first found to be 27.0mmol/L. Simultaneously run internal quality control samples yielded results that were within control limits. Repeat electrolytes analyses were carried out with the results showing consistently very high potassium values. For this reason, the consultant chemical pathologist was notified. Investigation in to the possible cause of the outrageous potassium result revealed that the whole blood specimen was collected with a "green-capped" specimen bottle which was later identified to be an EDTA specimen bottle.

Case 4 (Table 4): A blood sample from a 5-day old neonate was personally submitted to laboratory for electrolytes analyses by an house-officer working in the special baby care unit of a tertiary hospital. The sample was collected in a lithium heparin specimen bottle. The receptionist observed that the sample volume was "small and slightly pink in colour" following centrifugation and promptly notified the doctor that submitted the sample. On sample analysis, the plasma potassium concentration was found to be 6.9mmol/L. Repeat analyses yielded results close to 6.9mmol/L. Consequently, the consultant chemical pathologist was notified who made an impression of pseudohyperkalaemia due to *in vitro* sample haemolysis and advised for a repeat specimen collection and analysis. A repeated plasma potassium analysis of a freshly collected specimen devoid of *in vitro* haemolysis gave result of 3.4mmol/L.

CASE SERIES OF PSEUDOHYPERKALAEMIA

Table 1: (Case 1) Psuedohyperkalaemia due to *in vitro* potassium contamination of sample

	Parameter Name	Result Values	Unit	Normal Values
BIOCHEMISTRY	SODIUM	145.1	mmoI/L	135.00 - 148.00
	POTASSIUM	7.56	mmoI/L	3.50 - 5.50
	Chloride	99.7	mmoI/L	96.0 - 110.0
	Bicarbonate	39.5	mmoI/L	22.0 - 32.0

Table 2: (Case 2) Psuedohyperkalaemia due to preanalytical refrigeration of blood specimen

	Parameter Name	Result Values	Unit	Normal Values
BIOCHEMISTRY	SODIUM	134.0	mmoI/L	136.00 - 145.00
	POTASSIUM	11.6	mmoI/L	3.50 - 5.10
	Chloride	94.1	mmoI/L	98.0 - 107.0
	Bicarbonate	26.3	mmoI/L	23.0 - 29.0
	SERUM UREA NITROGEN	19.2	mg/dI	13.0 - 43.0
	UREA (mmoI/L)	3.26	mmoI/L	2.2 - 7.2
	Creatinine	1.0	mg/dI	0.60 - 1.40
	Creatinine (umoI/L)	88.40	umoI/L	53.03 - 123.76

Table 3: (Case 3) Psuedohyperkalaemia due to use of wrong specimen bottle

	Parameter Name	Result Values	Unit	Normal Values
BIOCHEMISTRY	SODIUM	134.5	mmoI/L	136.00 - 145.00
	POTASSIUM	27.0	mmoI/L	3.50 - 5.10
	Chloride	101.3	mmoI/L	98.0 - 107.0
	Bicarbonate	30.4	mmoI/L	23.0 - 29.0
	SERUM UREA NITROGEN	24.7	mg/dI	13.0 - 43.0
	UREA (mmoI/L)	4.20	mmoI/L	2.2 - 7.2
	Creatinine	1.2	mg/dI	0.60 - 1.40
	Creatinine (umoI/L)	106.08	umoI/L	53.04 - 123.76

Table 4: (Case 4) Psuedohyperkalaemia due to *in vitro* sample haemolysis

	Parameter Name	Result Values	Unit	Normal Values
BIOCHEMISTRY	SODIUM	138.0	mmoI/L	136.00 - 145.00
	POTASSIUM	6.9	mmoI/L	3.50 - 5.10
	Chloride	98.6	mmoI/L	98.0 - 107.0
	Bicarbonate	23.3	mmoI/L	23.0 - 29.0

DISCUSSION

Hyperkalaemia is a fairly common electrolyte abnormality especially among hospitalized patients[8]. It is a potential cause of morbidity and mortality. Both moderate hyperkalaemia (K^+> 6.5-7.5 mmol/L) and severe hyperkalaemia (K^+>7.5 mmol/L) are medical emergencies that require timely diagnosis and prompt treatment[9]. Major causes of hyperkalaemia include: redistribution of intracellular potassium to extracellular fluid (ECF), impaired renal potassium excretion, and inadvertent ingestion or infusion of potassium-containing tablets or infusions[2]. However, before a definitive diagnosis of hyperkalaemia is made, the possible occurrence of pseudohyperkalaemia should be ruled out. Pseudohyperkalaemia refers to the spurious elevation of plasma potassium concentration in otherwise normokalaemic individual without clinical or

electrocardiographic evidence of hyperkalaemia[10]. It is a well-known cause of misdiagnosis and inappropriate treatment of hyperkalaemia if unrecognized.

Our reported cases highlight few of the potential causes of pseudohyperkalaemia in contemporary clinical practice. Generally, the causes of pseudohyperkalaemia are extensive. It can occur as a result of poor or improper blood specimen collection techniques including: (1) fist clenching prior to venepuncture, (2) mechanical trauma to blood cells during specimen collection or transportation, (3) *in vitro* potassium contamination of collected blood specimen, (4) refrigeration or freezing of whole blood specimen prior to centrifugation, (5) chilling of whole blood specimen during transport, (6) use of pneumatic tubes for specimen transport, and (7) *in vitro* sample haemolysis[5,6].

Cases 1 and 3 illustrate how *in vitro* potassium contamination can lead to spurious or artifactual elevation of measured potassium concentration. The two cases were purely due to avoidable human errors. However, the fact remains that they can happen. In both cases, EDTA-based specimen bottles that commonly contain tripotassium EDTA (K_3EDTA) salt in a concentration of 1 to 2g/L of blood were inadvertently used to collect whole blood specimen for plasma electrolytes analysis. The "thorough washing and rinsing" of the EDTA bottle with methylated spirit in case 1 does not guarantee the absence of potassium contamination. Thus, such a practice is highly prohibited. The wrong use of EDTA bottle to collect blood specimen for plasma electrolytes analyses is a fairly common occurrence especially for specimens collected outside the phelebotomy unit of the clinical laboratory[4,11]. Adequate education of the concerned healthcare personnel on the use and misuse of specimen bottles will go a long way to forestall this relatively common source of laboratory error[11].

The second reported case of pseudohyperkalaemia occurred as a result of extracellular shift of potassium ions that is contained within the blood cells (more especially the red blood cells) even in the absence of obvious sample haemolysis after centrifugation. Potassium ions (K^+) are predominantly intracellular in all body cells. About 98% of total body K^+ are intracellular while the remainder is in the ECF[12]. The intracellular-extracellular K^+ gradient is maintained by the activity of the energy-dependent sodium-potassium adenosine triphophatase (Na^+/K^+ATPase) which also functions as a pump[13]. Being an enzyme, storage of collected whole blood sample at 2^0C to 4^0C in the refrigerator prior to separation inhibits the activity of Na^+/K^+ATPase which operates optimally at the normal body temperature of 37^0C[14]. Again, the cold temperature inhibits the glycolytic pathway which is the major source of ATP for cytosolic and membrane-bound red cell enzymes including Na^+/K^+ ATPase. Since Na^+/K^+ ATPase is an energy-dependent enzyme, inadequate ATP supply leads to its inactivation. The inactivation of the Na^+/K^+ pump allows K^+ to move out of the blood cells (mostly the red cells) along its concentration gradient even without haemolysis[14]. This causes factitious hyperkalaemia in the sample. It has been reported that plasma sample K^+ concentration increases by approximately 2.0mmol/L after 4hours of storage at 4^0C[1].

Case 4 demonstrates the role of *in vitro* sample haemolysis in the causation of pseudohyperkalaemia. As stated above, K^+ is located predominantaly within the blood cell including the red blood cells. Generally, slight or mild *in vitro* sample haemolysis may have little or no effect on most measured analytes in plasma. However, for substances that are predominantly intracellular like K^+, *in vitro* sample haemolysis even when slight in degree, causes appreciable rise in their plasma concentrations[15]. For K^+, haemolysis of 0.5% of RBCs has the potential to cause elevated plasma concentration by 0.5 mmol/L[1]. The degree of *in vitro* sample haemolysis is measured by the haemoglobin (Hb) concentration of the haemolyzed sample. Usually for every 100mg/dL of Hb that is present in a haemolyzed sample, K^+ concentration rises by 0.6%[1]. Slight sample haemolysis (Hb concentration$\simeq$50mg/dL), moderate sample haemolysis (Hb concentration $\simeq$200mg/dl) and gross sample haemolysis (Hb concentration > 500mg/dL) have been reported to increase K^+ concentration of an haemolyzed sample by 3%, 12%, and 30% respectively.[1] In practice, it is recommended that any visible *in vitro* sample haemolysis should be noted and reported as the possible cause of a falsely high measured K^+ concentration in the sample[16,17].

Beside the above reported causes of pseudohyperkalaemia, other notable causes include leakage of K^+ from blood cells in circumstances of excessive leucocytosis, thrombocytosis, and erythocytosis.[18] Pseudohyperkalaemia has been reported among patients with acute and chronic leukamias, thrombocytaemia, and polycythaemia[18,19].

CONCLUSION

The four reviewed cases highlight the three common causes of pseudohyperkalaemia in contemporary clinical practice. Pseudohyperkalaemia is a potential cause of increased measured plasma potassium concentration in the clinical laboratory. Thus, it must be ruled out before a definitive diagnosis of (true) hyperkalaemia is made. Pseudohyperkalaemia can be misleading and when unrecognized could lead to inappropriate and potentially harmful treatment. A high index of suspicion of pseudohyperkalaemia in all cases of moderate and severe hyperkalaemia is necessary for timely recognition and troubleshooting of this potentially harmful phenomenon.

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