Clinical Chemistry Trainee Council
Pearls of Laboratory Medicine
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TITLE: Hyperkalemia

PRESENTER: Roy W.A. Peake, PhD, FRCPath, DABCC

Slide 1:
Hello, my name is Roy Peake. I am a Research Fellow at the Department of Laboratory Medicine, Boston Children's Hospital. Welcome to this Pearl of Laboratory Medicine on "Hyperkalemia."

Hyperkalemia is a very commonly encountered electrolyte abnormality. As a result of its serious clinical implications, it is very important that laboratory staff are competent in recognizing true hyperkalemia when it occurs. The causes of hyperkalemia and approaches for its investigation will be discussed in this talk.

Slide 2:
Potassium is the most abundant cation in the body. The vast majority of body potassium is found within the intracellular compartment. In fact, only 2% is extracellular. In laboratory medicine, we are principally interested in the potassium concentration within the extracellular compartment. There is a tendency for potassium to diffuse down its concentration gradient from the intracellular to extracellular compartment. This process is opposed by the Sodium/Potassium/ATPase which works to keep potassium inside the cell. In adults, the plasma or serum potassium reference interval is typically 3.5 to 5.5 mmol/L. Disturbances in potassium distribution resulting in an increase in extracellular potassium concentration may be defined as hyperkalemia.

Slide 3:
By definition, hyperkalemia is a serum potassium concentration greater than the upper limit of the reference interval (e.g. >5.5 mmol/L). The clinical symptoms are dependent on the potassium concentration *per se*. However, the potassium concentration at which clinical symptomology occurs may vary widely from individual to individual and will depend on the underlying cause. Potassium concentrations less than 6.5 mmol/L are typically asymptomatic. However, concentrations > 6.5 mmol/L may be accompanied by clinical signs such as cardiac arrhythmias and ventricular tachycardia. In addition, characteristic ECG changes may be observed, such as peaked T waves, QRS broadening, and ST depression. Whatever the cause, marked hyperkalemia is a medical emergency that may result in cardiac arrest. Consequently, clinical laboratories should have a clear policy in place for telephoning elevated potassium results.

Slide 4:
In no particular order, here are some points that might be considered when investigating a case of hyperkalemia.

First, how elevated is the potassium concentration? Was there any relevant clinical information accompanying the request that might explain the hyperkalemia? How does this result compare with previous potassium results? Is the hyperkalemia acute or chronic in onset? What was the source of the request, for example, outpatients, inpatients, or perhaps from a renal ward or dialysis unit?

Second, could the hyperkalemia be artifactual? Artifactually elevated potassium in serum may be caused by sample hemolysis, delays in sample transit to the laboratory, sample contamination, or a cellular artifact, such as that seen from patients with elevated platelet or leucocyte counts. Is there any evidence of renal impairment?

And finally, is the patient taking any drugs that may be contributing to the hyperkalemia?

Slide 5:
This slide highlights an initial approach for the investigation of hyperkalemia. When attempting to ascertain the cause, the possibility of an artifactual result should always be considered, as this is very common. Examples of artifactual causes include hemolysis, delays in centrifugation, contamination, and pseudohyperkalemia caused by thrombocytosis/leucocytosis.

Slide 6:
Sample hemolysis (*in vitro* hemolysis) is caused by mechanical trauma to red blood cells during sample collection, resulting in K^+ release from the intracellular compartment. The degree of K^+ increase is dependent on the extent of hemolysis. Hemolysis is very common, especially in samples from certain patient groups, such as neonates, or wards, such as the Emergency Room. Another cause of hyperkalemia is delays in sample centrifugation. Over time, potassium leaks from the intracellular compartment down a concentration gradient to the extracellular compartment. Delays in sample centrifugation can result in a falsely increased K^+ concentration. This is a particular problem in samples received from primary care, where long distances may be involved in transporting samples to the laboratory. This is a temperature-dependent effect, where more K^+ leaks from cells at lower temperatures, due to inactivity of the Na^+/K^+/ATPase.

Slide 7:
The first type of contamination to consider is Potassium-EDTA contamination from a CBC vacutainer tube. This can occur when blood is drawn into a CBC vacutainer tube, immediately followed by blood draw into a serum vacutainer tube. This results in contamination of the serum sample with K^+/EDTA salt from the CBC tube. This typically causes a grossly increased serum potassium concentration. In addition, EDTA is a powerful chelator of divalent cations such as calcium, magnesium, and zinc. Therefore, in a serum sample contaminated with EDTA, calcium concentration is abnormally decreased. Alkaline phosphatase (ALP) activity is also typically decreased, since magnesium and zinc are important co-factors for this enzyme. Therefore, if K^+/EDTA contamination is suspected, calcium and ALP analysis on that sample may help to confirm this suspicion.

Slide 8:
Here is an example of a case of contamination with K^+/EDTA. Serum chemistry results are shown for a sample drawn from a patient on a routine visit to a hematology clinic. The results show a markedly increased potassium level. First of all, a potassium concentration of 11.0 mmol/L should immediately give a strong suspicion of contamination as a cause. The sample was not hemolysed and there was no delay in centrifugation. The markedly decreased calcium concentration and decreased ALP activity is highly suggestive of K^+/EDTA contamination. On discussion with the clinical team, an urgent follow-up sample was drawn for repeat chemistry analysis. This second sample produced results for all three analytes within the reference interval, confirming the suspicion of contamination of the original sample.

Slide 9:
Another form of sample contamination to consider is that from potassium-containing intravenous fluids. Potassium is often given with dextrose. Therefore, a markedly raised glucose level may raise the index of suspicion of contamination. Another artifactual cause of hyperkalemia is the presence of elevated platelets or leucocytes in a serum sample from a patient with thrombocytosis or leucocytosis. In thrombocytosis, platelets are released during the clotting process resulting in pseudohyperkalemia (this is not a true indicator of physiological blood potassium concentration). Pseudohyperkalemia observed in a serum sample caused by elevated platelets can be resolved by measuring potassium in a plasma sample instead, where no clotting has occurred.

Slide 10:
Here is an example of a case of pseudohyperkalemia caused by thrombocytosis. Post-operative bloods were drawn from a patient in a general surgery ward. The results show hyperkalemia on a non-hemolysed sample. The patient was clinically well with no ECG changes, so the results did not appear to fit clinically. The platelet count was noted to be elevated at 1428 $x10^9$/L. The medical team was contacted and another sample was drawn from the patient, this time collected into a lithium heparin plasma tube. The plasma potassium result was 4.4 mmol/L. Pseudohyperkalemia was confirmed due to thrombocytosis.

Slide 11:
This graph highlights the variation of plasma and serum potassium levels with corresponding platelet count monitored in this patient over a 10-day period. The differences between the plasma and serum potassium concentrations are highly significant.

Slide 12:
Another important cause of hyperkalemia to consider is renal retention of potassium. This can occur due to acute and chronic renal failure, or hypoaldosteronism.

Slide 13:
In chronic renal failure, hyperkalemia occurs as a result of increased renal K^+ retention due to decreased Glomerular Filtration Rate. This is commonly encountered in dialysis patients. In acute renal failure,

there may be potassium release from the intracellular compartment as a result of acute tubular necrosis. Metabolic acidosis in renal failure may also drive hyperkalemia. In hypoaldosteronism, decreased aldosterone production by the adrenal cortex results in renal potassium retention and subsequent hyperkalemia. This may occur in primary or secondary adrenal failure.

Slide 14:

Here is an example of a case of hypoaldosteronism secondary to primary adrenal failure. A 38-year-old female presents to the ER overnight complaining of general malaise, vomiting, and abdominal pain. The following bloods were taken at approximately 8AM. In addition to the hyperkalemia, the results show an inappropriately low 8AM cortisol value, hyponatremia, and pre-renal uraemia. This patient has primary adrenal failure (Addison's Disease). Decreased aldosterone production by the adrenal cortex results in renal potassium retention and subsequent hyperkalemia.

Slide 15:

This cartoon attempts to summarize the renin-angiotensin system. In response to hypotension, the juxtaglomerular cells of the kidney release renin into the plasma, which catalyzes the conversion of angiotensinogen to angiotensin I. Angiotensin I is converted to angiotensin II by angiotensin converting enzyme from the lungs. Angiotensin II stimulates the release of aldosterone from the adrenal cortex, which acts on the renal collecting duct to excrete K+. Angiotensin Converting Enzyme Inhibitors (ACE) inhibitors prevent the production of angiotensin II thereby removing the aldosterone-mediated excretion of K+, resulting in renal retention of the latter and subsequent hyperkalemia.

Slide 16:

Another important cause of hyperkalemia to consider is drug therapy. Drugs that can elevate K^+ include K^+ sparing diuretics, Angiotensin Converting Enzyme Inhibitors (ACEis), Angiotensin Receptor Blockers (ARBs), B-blockers, and Heparin.

Slide 17:

Potassium-sparing diuretics may cause hyperkalemia, common examples of which include Amiloride and Spironolactone. These drugs have traditionally been prescribed for heart failure and hypertension. Spironolactone is an aldosterone antagonist which inhibits sodium reabsorption at the collecting duct with concurrent potassium retention. Amiloride blocks the epithelial sodium channel promoting sodium and water loss with potassium retention. Angiotensin Converting Enzyme Inhibitors (ACE-inhibitors) can also cause hyperkalemia. Some commonly used examples include Ramipril and Lisinopril. These drugs are commonly prescribed for hypertension. They act on the Renin-Angiotensin system and inhibit aldosteronism promoting renal potassium excretion. ACE-inhibitors are recommended for use in patients with chronic kidney disease.

Slide 18:

Another cause to consider is the transcellular shifting of potassium. This may be due to metabolic acidosis, cellular Lysis and tissue anoxia, or lack of insulin states.

Slide 19:

In metabolic acidosis, there is an increase in extracellular hydrogen ion concentration. To maintain electroneutrality, H^+ ions will "shift" into the intracellular compartment. In exchange, K^+ ions "shift" into the extracellular compartment, causing hyperkalemia. In cell Lysis, potassium is released from the intracellular compartment, as may occur in rhabdomyolysis or acute intravascular hemolysis. Finally, states of hypoinsulinemia (e.g. Diabetic Ketoacidosis) may result in hyperkalemia. This is because insulin is required to "shift" potassium into the cell.

Slide 20:

The management of hyperkalemia may require urgent or conservative action. Urgent potassium reduction is required if $[K^+] > 7.0$ mmol/L or if there are significant ECG changes. This is typically done by slow IV infusion of insulin/dextrose which lowers the serum $[K^+]$ concentration by shifting potassium into the intracellular compartment. Calcium gluconate may also be given intravenously in order to stabilize the myocardium. For less urgent potassium reduction (typically when $[K^+]$ is between 6.5 and 7.0 mmol/L or if there are no significant ECG changes), ion exchangers may be used (e.g. Resonium: lowers $[K^+]$ by exchanging sodium for potassium).

Slide 21: Disclosures

Slide 22: Thank You from www.TraineeCouncil.org

Thank you for joining me on this Pearl of Laboratory Medicine on "Hyperkalemia". I am Roy Peake.