Hyperkalemia
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Potassium (K\(^+\)) is the most abundant cation in the body. The vast majority is found in the intracellular compartment (~2\% is extracellular). Potassium is maintained inside the cell by the Na\(^+\)/K\(^+\)/ATPase. Serum adult reference interval is ~3.5 to 5.5 mmol/L. Disturbances in K\(^+\) distribution resulting in an increase in extracellular K\(^+\) concentration is defined as hyperkalemia.
Hyperkalemia

- Serum $[K^+] > 5.5$ mmol/L
- Clinical symptoms depend upon the serum/plasma $[K^+]$
- Clinical symptoms also depend upon the underlying cause
  - $[K^+]$ 5.6 to 6.5 mmol/L - Usually asymptomatic
  - $[K^+] > 6.5$ mmol/L - May result in cardiac arrhythmias and ventricular tachycardia

- In addition to clinical symptoms, characteristic ECG changes may be observed (peaked T waves, broadening of QRS complex, ST depression)
- Marked hyperkalemia is a life-threatening emergency
- May result in cardiac arrest
- **Clinical laboratories should have a clear policy in place for telephoning elevated serum/plasma $K^+$ results**
Investigation: Points to Consider

➢ How elevated is the serum $[K^+]$?
➢ Clinical information?
➢ Comparison with previous results where available
➢ Acute or chronic?
➢ Source of the request (e.g. inpatient/outpatient/renal unit)

➢ Could the result be artifactual?
  ▪ Hemolysis
  ▪ Time taken for sample to get to the laboratory
  ▪ Contamination of sample
  ▪ Pseudohyperkalemia resulting from elevated platelets or leucocytes

➢ Renal function?
➢ Drug history?
Investigation of Hyperkalemia 1

HYPERKALEMIA

↓

Causes of elevated $[K^+]$ → Eliminate artifactual causes

↓

1. Hemolysis
2. Delays in centrifugation
3. Contamination
4. Elevated platelets or leukocytes

Very important that the laboratory works to identify artifactual causes of hyperkalemia
Artifactual Causes

➢ Sample Hemolysis
  ▪ Sample hemolysis (*in vitro*) is caused by mechanical trauma to red blood cells during collection
  ▪ $K^+$ released from intracellular compartment
  ▪ The degree of $K^+$ increase is dependent on the extent of hemolysis
  ▪ Very common, especially in samples from certain patient groups (e.g. neonates) or wards (Emergency Room)

➢ Delays in Sample Centrifugation
  ▪ Over time, $K^+$ leaks from cells
  ▪ Delays in centrifugation can result in falsely increased serum $[K^+]$
  ▪ This is a particular problem in samples received from primary care where long distances may be involved in transporting samples
  ▪ This effect is temperature-dependent (more $K^+$ leaks from cells at low temperatures due to inactivity of the $Na^+/K^+/ATPase$)
Artifactual Causes

- Contamination of specimen with K⁺/EDTA
  - Occurs when blood is drawn into a CBC vacutainer followed by a serum vacutainer tube, resulting in contamination of the serum sample with K⁺/EDTA
  - Typically causes a grossly increased serum K⁺ concentration
  - EDTA is a chelator of divalent cations such as calcium, magnesium, and zinc
  - In a sample contaminated with EDTA, calcium concentration is abnormally decreased
  - Alkaline phosphatase (ALP) activity is also typically decreased since the chelated magnesium and zinc ions are important co-factors for this enzyme
  - Therefore, if K⁺/EDTA contamination is suspected, calcium and ALP analysis on that sample may help confirm this suspicion
Case A

- Routine pre-chemotherapy bloods from hematology clinic:

<table>
<thead>
<tr>
<th></th>
<th>Value</th>
<th>Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium</td>
<td>140 mmol/L</td>
<td>(137 – 144)</td>
</tr>
<tr>
<td>Potassium</td>
<td>11.0 mmol/L</td>
<td>(3.5 – 4.9)</td>
</tr>
<tr>
<td>Chloride</td>
<td>109 mmol/L</td>
<td>(98 – 106)</td>
</tr>
<tr>
<td>Urea</td>
<td>11.4 mmol/L</td>
<td>(3.4 - 7.0)</td>
</tr>
<tr>
<td>Creatinine</td>
<td>76 µmol/L</td>
<td>(84 - 116)</td>
</tr>
<tr>
<td>Calcium (Adjusted)</td>
<td>1.40 mmol/L</td>
<td>(2.20 – 2.26)</td>
</tr>
<tr>
<td>Albumin</td>
<td>3.6 g/dL</td>
<td>(3.7 – 4.9)</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>5 µmol/L</td>
<td>(1 – 22)</td>
</tr>
<tr>
<td>ALT</td>
<td>21 U/L</td>
<td>(&lt;40)</td>
</tr>
<tr>
<td>ALP</td>
<td>41 U/L</td>
<td>(45 – 105)</td>
</tr>
</tbody>
</table>

- Sample was NOT hemolysed and no delay in sample centrifugation
- Grossly increased $K^+$ and decreased calcium and Alkaline phosphatase
- Results consistent with contamination with $K^+$/EDTA from CBC tube
- On repeat blood draw, $K^+$ (3.8 mmol/L); Calcium (2.19 mmol/L); ALP (95 U/L)
Artifactual Causes

- Contamination of specimen from I.V. fluid
  - Contamination from intravenous fluid containing potassium
  - $K^+$ is often given with dextrose
  - A markedly elevated glucose result may raise the index of suspicion

- Elevated platelets or leucocytes
  - May be observed in serum samples from patients with thrombocytosis or leukocytosis
  - In thrombocytosis, platelets are released during the clotting process resulting in pseudohyperkalemia (this is not a true indicator of physiological blood $K^+$ concentration)
  - Pseudohyperkalemia observed in a serum sample caused by elevated platelets can be resolved by measuring $K^+$ in a plasma sample (no clotting) instead
Case B

➢ Post-operative bloods from a patient on a general surgery ward

<p>| | | | |</p>
<table>
<thead>
<tr>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium</td>
<td>136</td>
<td>mmol/L</td>
<td>(137 – 144)</td>
</tr>
<tr>
<td>Potassium</td>
<td>7.0</td>
<td>mmol/L</td>
<td>(3.5 – 4.9)</td>
</tr>
<tr>
<td>Chloride</td>
<td>96</td>
<td>mmol/L</td>
<td>(98 – 106)</td>
</tr>
<tr>
<td>Urea</td>
<td>6.2</td>
<td>mmol/L</td>
<td>(3.4 - 7.0)</td>
</tr>
<tr>
<td>Creatinine</td>
<td>47</td>
<td>µmol/L</td>
<td>(84 - 116)</td>
</tr>
</tbody>
</table>

➢ Hyperkalemia on a non-hemolysed specimen
➢ Patient was clinically well with no ECG changes (results did not fit clinically)
➢ Platelet count was noted to be elevated: 1428 x10^9/L (140 – 400x10^9/L)
➢ The medical team were contacted and another sample was drawn from the patient collected into a lithium heparin plasma tube
➢ Plasma K⁺ result returned was 4.4 mmol/L
➢ Pseudohyperkalemia confirmed due to thrombocytosis
Figure 1: Variation of plasma and serum potassium in a patient with thrombocytosis.
Investigation of Hyperkalemia 2

HYPERKALEMIA

Causes of elevated $[K^+]$

Eliminate artifactual causes

1. Hemolysis
2. Delay in centrifugation
3. Contamination
4. Elevated platelets or leukocytes

Renal Retention

1. Acute renal failure
2. Chronic renal failure
3. Hypoadrenalism (e.g. adrenal failure)
Renal Retention

➢ Renal Failure
  ▪ Hyperkalemia occurs in chronic renal failure as a result of decreased Glomerular Filtration Rate and subsequent increase in renal K⁺ retention
  ▪ Commonly encountered in dialysis patients
  ▪ In acute renal failure, there may be K⁺ release from the intracellular compartment as a result of acute tubular necrosis
  ▪ Metabolic acidosis in renal failure may also drive hyperkalemia

➢ Hypoadrenalism
  ▪ Decreased aldosterone production by the adrenal cortex results in renal K⁺ retention and subsequent hyperkalemia
  ▪ May occur in primary or secondary adrenal failure
A 38 year old female presents to the ER complaining of general malaise, vomiting and abdominal pain. The following bloods were taken around 8am:

- Sodium: 121 mmol/L (137 – 144)
- Potassium: 5.8 mmol/L (3.5 – 4.9)
- Chloride: 99 mmol/L (98 – 106)
- Urea: 13.0 mmol/L (3.4 - 7.0)
- Creatinine: 88 μmol/L (84 - 116)
- Cortisol: <50 nmol/L

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 K⁺ retention and subsequent hyperkalemia.
Case C

Angiotensinogen → Angiotensin I → Angiotensin II

Renin

Lungs

ACE inhibitors

Angiotensin Converting Enzyme

Adrenal Cortex

Aldosterone

Hypotension

Sodium depletion

Kidney

Renal K⁺ excretion

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Investigation of Hyperkalemia 3

HYPERKALEMIA

Causes of elevated $[K^+]$

Eliminate artifactual causes

1. Hemolysis
2. Delay in centrifugation
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Renal Retention

1. Acute renal failure
2. Chronic renal failure
3. Hypoaldosteronism (e.g. adrenal failure)

Drug therapy

1. $K^+$ sparing diuretics (e.g. spironolactone)
2. Angiotensin Converting Enzyme Inhibitors (ACEis)
3. Angiotensin Receptor Blockers (ARBs)
4. B-blockers
5. Heparin
Drug therapy

➢ Potassium-sparing diuretics
  ▪ E.g. Spironolactone and Amiloride
  ▪ These drugs are K⁺ sparing diuretics traditionally prescribed for heart failure and hypertension
  ▪ Spironolactone is an aldosterone antagonist which inhibits sodium reabsorption at the collecting duct with concurrent K⁺ retention
  ▪ Amiloride is used as an blocks the epithelial sodium channel promoting sodium and water loss with K⁺ retention

➢ Angiotensin Converting Enzyme Inhibitors (ACEis)
  ▪ E.g. Ramipril and Lisinopril
  ▪ ACEis are commonly prescribed for hypertension
  ▪ Act on the Renin-Angiotensin system and inhibit aldosteronism promoting renal K⁺ excretion
  ▪ ACEis are recommended for use in patients with CKD
Investigation of Hyperkalemia

**HYPERKALEMIA**

Causes of elevated [K⁺]

- **Renal Retention**
  1. Acute renal failure
  2. Chronic renal failure
  3. Hypoaldosteronism
  4. (e.g. adrenal failure)

- **Drug therapy**
  1. K⁺ sparing diuretics e.g. spironolactone
  2. ACEis
  3. ARBs
  4. B-blockers
  5. Heparin

- **Transcellular K⁺ movement**
  1. Metabolic acidosis
  2. Cellular Lysis e.g. Rhabdomyolysis, intravascular (in-vivo) hemolysis
  3. Anoxia
  4. Lack of insulin (e.g. DKA)

Eliminate artifactual causes

- 1. Hemolysis
- 2. Delay in centrifugation
- 3. Contamination
- 4. Elevated platelets or leukocytes
Transcellular K⁺ “Shifting”

➢ Metabolic Acidosis
  ▪ In acidosis states there is an increase in extracellular [H⁺]
  ▪ To maintain electroneutrality, H⁺ ions will diffuse or “shift” across the cell membrane from the extracellular to the intracellular compartment
  ▪ In exchange, K⁺ ions will move in the opposite direction from the intracellular to extracellular compartment, causing hyperkalemia

➢ Cell Lysis
  ▪ K⁺ release from the intracellular compartment e.g. Rhabdomyolysis or acute intravascular hemolysis (*in vivo* hemolysis)

➢ Lack of Insulin
  ▪ Insulin is required to “shift” K⁺ into the cell
  ▪ States of hypoinsulinemia (e.g. DKA) may result in hyperkalemia
Management of Hyperkalemia

➢ Urgent potassium reduction
  ▪ Required if [K+] > 7.0 mmol/L
  ▪ Required if there are significant ECG changes
  ▪ Typically by slow IV infusion of insulin/dextrose (lowers serum [K+] by shifting K⁺ into the intracellular compartment)
  ▪ Calcium gluconate may also be given intravenously in order to stabilize the myocardium

➢ Less urgent potassium reduction
  ▪ Typically when [K+] between 6.5 and 7.0 mmol/L
  ▪ No significant ECG changes
  ▪ Ion exchangers may be used (e.g. Resonium – lowers [K+] by exchanging sodium for K⁺)
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