RATIONAL TESTING

Investigating hypokalaemia

Richard A Oram specialist registrar and Diabetes UK clinical training fellow1 4, Timothy J McDonald principal clinical scientist and National Institute for Health Research CSO fellow2 4, Bijay Vaidya consultant endocrinologist and honorary associate professor (reader)3

1Department of Renal Medicine, Royal Devon and Exeter Hospital, Exeter, UK; 2Department of Blood Sciences, Royal Devon and Exeter Hospital, Exeter, UK; 3Department of Endocrinology, Royal Devon and Exeter Hospital and University of Exeter Medical School, Exeter EX2 5DW, UK; 4NIHR Exeter Clinical Research Facility, University of Exeter Medical School, Exeter, UK

This series of occasional articles provides an update on the best use of key diagnostic tests in the initial investigation of common or important clinical presentations. The series advisers are Steve Atkin, professor, head of department of academic endocrinology, diabetes, and metabolism, Hull York Medical School; and Eric Kilpatrick, honorary professor, department of clinical biochemistry, Hull Royal Infirmary, Hull York Medical School. To suggest a topic for this series, please email us at practice@bmj.com.

A 22 year old woman had a blood test to investigate lethargy at her general practice surgery and was found to have an isolated low serum potassium (2.6 mmol/L; 1 mmol/L=1mEq/L). Her blood pressure was 110/70 mm Hg, and physical examination showed no abnormalities. She was taking no regular drugs and denied taking liquorice or laxatives. She had no recent history of vomiting or diarrhoea.

What is the next investigation?

Background

Hypokalaemia is defined as a serum potassium below 3.5 mmol/L and is commonly graded as mild (3.1-3.5 mmol/L), moderate (2.5-3.0 mmol/L), and severe (<2.5 mmol/L).1 Hypokalaemia is a common finding in the general population; a community based cohort study of 5200 adults over 55 years in the Netherlands showed a 3% prevalence of mild hypokalaemia.2 It is much more common in hospital populations, with one episode of severe hypokalaemia per week in an observational study at a UK secondary care hospital with a catchment population of 150 000.3

About 98% of the body’s potassium is intracellular,4 and the intracellular-extracellular potassium gradient is crucial to maintaining resting membrane potential and normal nerve and muscle function. Small decreases in extracellular potassium can have serious effects on the heart and skeletal muscles. Mild hypokalaemia is often asymptomatic and picked up on routine blood tests, but severe hypokalaemia is associated with life threatening arrhythmias and sudden cardiac death. In a double blind randomised controlled trial, hypertensive men treated with thiazide diuretics who developed a serum potassium of 3 mmol/L or less had a twofold increase in ventricular arrhythmias compared with those with normal serum potassium.5

Is the patient safe?

Because severe hypokalaemia can cause fatal arrhythmias, the first question to answer is whether the patient is in immediate danger (figure↓). If serum potassium is severely low (<2.5 mmol/L), or if there are symptoms of severe hypokalaemia (such as muscle weakness, syncope, or palpitations), evaluate and treat the patient urgently in an acute facility with cardiac monitoring.6 Initial assessment of moderate or severe hypokalaemia should include electrocardiography, which may show small T waves, ST depression, prominent U waves, or a prolonged QT interval. Patients with rapid onset of hypokalaemia, concomitant risk factors (especially digoxin treatment, left ventricular hypertrophy, or heart failure), and electrocardiographic changes are at increased risk of serious arrhythmias.7

The next step is to take a detailed history and examination of the patient. The main laboratory investigations are assessment of serum and urine electrolytes and acid-base balance.

History

The history often helps clarify the likely cause of hypokalaemia. Gastrointestinal symptoms and a history of diuretic treatment are important because a retrospective observational study found that most cases of hypokalaemia are associated with vomiting or diarrhoea (51%) or diuretics (47%).8 Reduced oral intake alone rarely causes hypokalaemia in healthy people but is a contributing factor in more than a third of inpatients with severe hypokalaemia.9 Also ask about a history of excessive alcohol intake, chronic laxative misuse, or liquorice ingestion.
Any process that stimulates uptake of potassium from the extracellular fluid into cells can cause hypokalaemia. This is common after intravenous insulin for treatment of hyperglycaemia (in particular, diabetic ketoacidosis), but stimulation of sympathetic f2 receptors (for example, with high dose salbutamol) and verapamil overdose can have a similar effect. Uptake of potassium by rapidly dividing cells—for example, after vitamin B3 deficiency or folate replacement in megaloblastic anaemia—can also cause hypokalaemia. In patients with a history of muscle weakness (typically after strenuous exercise or a large carbohydrate meal) and severe hypokalaemia, consider the possibility of hypokalaemic periodic paralysis or thyrotoxic periodic paralysis (if symptoms of thyrotoxicosis are also present, particularly in Asian men).

Physical examination

Look for flaccid muscle weakness and signs of arhythmias. Check blood pressure because hypertension in association with hypokalaemia may suggest primary hyperaldosteronism or Cushing’s syndrome. In this last scenario, clinical features of steroid excess—such as central obesity, bruises, and proximal muscle weakness or wasting—may be evident. Signs of dehydration, hypotension, and Kussmaul breathing in a patient with diabetes are suggestive of diabetic ketoacidosis.

Laboratory investigations

In mild hypokalaemia with an obvious cause, laboratory investigations will be limited to monitoring serum potassium concentrations. However, if hypokalaemia is moderate or severe, or the cause of hypokalaemia is unclear, initial basic laboratory investigations should include sodium, potassium, creatinine, urea, magnesium, glucose, and bicarbonate (figure). Spurious hypokalaemia may occur due to in vitro redistribution—for example, potassium uptake by large numbers of abnormal white cells in leukaemia when the sample is left at room temperature. If this is suspected, send a fresh blood sample to the laboratory for reanalysis of potassium, making sure that the sample arrives rapidly after venepuncture.

Assessment of acid-base balance

Measurement of serum bicarbonate can help assess acid-base balance. Acutely, bicarbonate is low in metabolic acidosis and high in metabolic alkalosis, but interpretation can be difficult in chronic compensated acid-base disorders. In this last situation, analysis of arterial blood gases allows complete assessment of respiratory and metabolic components of acid-base disturbance.8 The table summarises common acid-base disorders associated with hypokalaemia. Diarrhoea and other low gastrointestinal disorders (including laxative misuse) can cause hypokalaemia and metabolic acidosis due to direct potassium and bicarbonate loss. Diabetic ketoacidosis is also associated with metabolic acidosis, whereas renal potassium wasting (see below) with acidosis points towards renal tubular acidosis as a possible cause. Conversely, excessive vomiting leads to metabolic alkalosis and hypokalaemia (from potassium loss in vomit, aldosterone dependent sodium reabsorption in response to hypovolaemia, and reabsorption of hydrogen ions in response to alkalosis at the expense of potassium loss in the distal nephron). In addition, low serum chloride is common after chronic vomiting, owing to direct loss of chloride. Hypokalaemia associated with alkalosis also occurs in patients taking diuretics; patients with mineralocorticoid excess; and disorders such as Bartter’s syndrome, Gitelman’s syndrome, and Liddle’s syndrome, which are caused by mutations in the diuretic sensitive ion transporters.

Assessment of renal potassium loss

Assessment of urine potassium can help to determine whether hypokalaemia is due to renal potassium loss, when the cause is not obvious. A spot urine potassium, 24 hour urine potassium, transtubular potassium gradient, and urine potassium:creatinine ratio (KCR) can all be used to assess renal potassium loss. One small study showed that a urine KCR of 2.5 mmol/mmol or more was accurate at discriminating hypokalaemia due to renal potassium wasting from a non-renal cause.9 Urine KCR performs better than a random urine potassium concentration alone, without the need for 24 hour collections of urine, and is the most practical way to assess renal potassium loss. Diuretics are the most common cause of hypokalaemia due to renal loss of potassium. Rarer causes that should be considered when the common causes are excluded include renal diseases such as renal tubular acidosis (often associated with autoimmune diseases such as Sjögren’s syndrome) or hereditary renal tubular disorders (such as Bartter’s or Gitelman’s syndrome).

Assessment of magnesium

An assessment of serum magnesium is important because hypokalaemia and hypomagnesaemia often coexist, and treatment of hypokalaemia is unlikely to be successful without reversal of hypomagnesaemia.10 Check magnesium if the cause of hypokalaemia is not obvious or hypokalaemia is moderate to severe.

When to refer?

Severe hypokalaemia warrants referral to an acute hospital. Refer patients with ongoing hypokalaemia with no explanation for specialist endocrine or renal assessment.

Other specialised tests

After referral, specialised tests are sometimes needed to determine the cause of hypokalaemia. The assessment of plasma aldosterone to renin ratio is considered the most reliable tool for investigating primary hyperaldosteronism, with a retrospective study showing a sensitivity and specificity of 97% and 94%, respectively.11 This ratio is raised in primary hyperaldosteronism and should be assessed in patients presenting with hypertension and unexplained hypokalaemia. Patients with hypokalaemia and clinical features of steroid excess should undergo screening tests (such as 24 hour urinary cortisol, overnight dexamethasone suppression test, or midnight
salivary cortisol) for Cushing’s syndrome. Check thyroid function tests (serum thyroid stimulating hormone and free thyroxine) if thyrotoxic periodic paralysis is suspected.

Outcome

The patient was referred to a renal clinic for assessment and was found to have high serum bicarbonate (34 mmol/L; reference range 22-30). Hypokalaemia and metabolic alkalosis fitted with either upper gastrointestinal potassium loss or renal potassium loss due to diuretics, Bartter’s syndrome, or Gitelman’s syndrome. A normal blood pressure made mineralocorticoid excess an unlikely cause. A urinary KCR of less than 2.5 mmol/mmol suggested non-renal potassium loss. Serum chloride was low at 84 mmol/L (reference range 95-108), which fitted with upper gastrointestinal fluid loss. On closer questioning, with the knowledge of these results, the patient confessed to recurrent self-induced vomiting to help with weight loss.

Thanks to James Forrer and Hannah Oram (general practitioners), Junaid Zaman (cardiologist), and Rhian Clissold (renal physician) for their helpful comments on the manuscript.

Contributors: RAO wrote the first draft of the manuscript; all authors revised the manuscript and approved the final version. BV is guarantor.

Competing interests: We have read and understood the BMJ Group policy on declaration of interests and declare the following interests: None.

Provenance and peer review: Commissioned; externally peer reviewed.

Patient consent not required (patient anonymised, dead, or hypothetical).


Cite this as: BMJ 2013;347:f5137
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### Table

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<tr>
<th>Type of disturbance</th>
<th>Key feature</th>
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<tr>
<td><strong>Hypokalaemic acidosis</strong></td>
<td></td>
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<tr>
<td>Diarrhoea, laxative misuse, and other lower gastrointestinal loss</td>
<td>Normal serum chloride</td>
</tr>
<tr>
<td>Diabetic ketoacidosis</td>
<td>High ketones; potassium drops after intravenous insulin is administered</td>
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<tr>
<td>Renal tubular acidosis</td>
<td>Associated with autoimmune disease (type 1) and Fanconi’s syndrome (type 2)</td>
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<tr>
<td><strong>Hypokalaemic alkalosis</strong></td>
<td></td>
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<tr>
<td>Vomiting and other upper gastrointestinal loss</td>
<td>Low serum chloride</td>
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<tr>
<td>Mineralocorticoid excess (such as primary hyperaldosteronism)</td>
<td>High blood pressure</td>
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<tr>
<td>Hereditary renal channelopathies:</td>
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<tr>
<td>Bartter’s syndrome</td>
<td>Presents in childhood</td>
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<tr>
<td>Gitelman’s syndrome</td>
<td>Often asymptomatic, presents in adulthood</td>
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<tr>
<td>Liddle’s syndrome</td>
<td>High blood pressure, low renin and aldosterone</td>
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<td>Diuretic use</td>
<td>Drug history</td>
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Algorithm for investigation and management of hypokalaemia. DKA, diabetic ketoacidosis; RTA, renal tubular acidosis