CASES IN PRIMARY CARE LABORATORY MEDICINE

Spurious hyperkalaemia

W Stuart A Smellie

Clinical Laboratory, Bishop Auckland General Hospital, Bishop Auckland DL14 6AD
info@smellie.com

BMJ 2007:334:693-5
doi:10.1136/bmj.39119.607986.47

Although severe hyperkalaemia is a life threatening medical emergency, spurious hyperkalaemia (pseudohyperkalaemia) is common in blood samples taken in primary care, often because of sampling conditions and storage and transport problems

Pseudohyperkalaemia can cause major difficulties in primary care and is a source of avoidable emergency referral and even admission to hospital. It poses a particular problem in the context of out of hours services, when not all patient information is necessarily available to on-call doctors, and is a source of serious concern to patients. This article examines two situations in which apparently alarming hyperkalaemia may occur; it offers guidance to minimise the problem of pseudohyperkalaemia caused by in vitro release of potassium and on identifying the less common causes due to other disease.

Case 1

A doctor responsible for clinical governance in a primary care practice contacted her local biochemistry laboratory to ask whether the laboratory had been experiencing problems with potassium measurement. Her practice partners had noticed several unexpectedly raised potassium results and one patient had recently been contacted urgently at 9 pm to be taken to hospital because a potassium result of 7.2 mmol/l had been telephoned to the out of hours service. This 72 year old man was being treated with lisinopril for hypertension and his previous potassium results had been in the region of 4.5-5.0 mmol/l. A repeat measurement in casualty had been 4.8 mmol/l and he had returned home in some distress.

The laboratory found that the average serum potassium result for that practice was 0.5 mmol/l above the laboratory's average for samples from general practice and that average results for the month were 0.3 mmol/l higher than in the previous three months. The practice was located 28 miles from the laboratory and was the first to be visited by the van on a circular collection run. During a recent winter cold spell, temperatures during the early evening, when the samples were being collected, had fallen to –3°C. Samples were held in a metal box in the van. An insulated box was introduced to transport specimens, and the average for the practice fell to 0.1 mmol/l above the laboratory's average.

SUMMARY POINTS

- True hyperkalaemia is rare in the presence of normal renal function
- Difficult venepuncture, cold storage, and deterioration of the sample all raise the serum potassium concentration and warm ambient temperature can lower it
- Thrombocytosis can raise serum potassium
- Severe leucocytosis can either raise or lower serum potassium depending on temperature
- Repeat sampling when results are suspect can avoid the distress of urgent hospital referral, at the same time excluding dangerous hyperkalaemia
- A full blood count and parallel measurements of serum and plasma (lithium heparin) potassium are useful to identify spurious hyperkalaemia arising from intrinsic causes (blood dyscrasias, red cell abnormalities)

Case 2

A 66 year old woman attended her doctor after having dysuria for three days. She was otherwise fit and was taking no regular medication. Her temperature and blood pressure were normal and examination was unremarkable. Urine dipstick testing was positive for leucocytes, nitrites, and blood.

Her doctor diagnosed an uncomplicated lower urinary tract infection and gave her a course of amoxicillin. He also checked her renal function. Results were returned as sodium 142 mmol/l, potassium 6.5 mmol/l, bicarbonate 26 mmol/l, urea 7.1 mol/l, creatinine 90 µmol/l, estimated glomerular filtration rate 57 ml/min/1.73 m^2. A creatinine measurement three months earlier had been 96 µmol/l.

The doctor repeated testing two days later and results were similar overall: potassium was 6.5 mmol/l and creatinine 84 µmol/l (estimated glomerular filtration rate 61 ml/min/1.73 m^2). He telephoned the laboratory for advice and was asked to send a third

This is the 11th article in this series

Box 1 | Causes of pseudohyperkalaemia

Related to collection and storage of specimen:

- Difficulty in collecting sample
- Patient clenched fist when sample was taken
- Sample was shaken or squirted through needle into collection tube
- Contamination with anticoagulant from another sample (potassium EDTA)
- Cooling
- Deterioration of specimen due to length of storage

Pre-existing conditions:

- Thrombocytosis
- Severe leucocytosis (which can also produce pseudohypokalaemia)
- Hereditary and acquired red cell disorders

sample, paired with a lithium heparin anticoagulated sample, for measurement of plasma potassium and a full blood count.

The serum potassium measurement from the third sample was similar to the previous result (6.3 mmol/l), but the anticoagulated sample had a plasma potassium of 5.1 mmol/l. The full blood count showed a white cell count of 33×10^9/l. The accompanying blood film report described appearances consistent with chronic lymphocytic leukaemia. The patient was referred urgently for a haematological opinion.

Discussion

In most cases spurious hyperkalaemia occurs during the collection, transport, or storage of specimens. The practitioner must decide whether a result is valid and whether urgent action is needed.[1]

Problems in samples

Box 1 shows the common causes of pseudohyperkalaemia. It is useful to record difficult venepuncture for future reference purposes, and fist clenching or shaking of samples should be avoidable with appropriate education for the person taking the sample. When syringes and needles are used, forcibly expressing blood through the collection needle into the collection tube can haemolyse blood, increasing the potassium concentration.

Spurious results relating to temperature or storage can be more problematic. The response of whole blood to temperature varies. A fall in the serum potassium concentration is seen when samples are stored at temperatures that are warm (25-30°C) but not sufficiently hot to cause sample deterioration (as a result of stimulation of the red cell membrane ATPase, which regulates exchange of potassium for sodium ions between the potassium rich intracellular environment and the relatively low potassium concentration in serum).

Average laboratory results for serum and plasma potassium in samples obtained from primary care have been reported to fall by up to 0.5 mmol/l in summer's high ambient temperatures.[2] This effect may be greater with serum.[3] Higher temperatures or long storage (overnight, for example) may lead to deterioration of the sample and large rises in potassium, although potassium stored at an ambient temperature of 18°C for up to 16 hours has been reported to be stable.[4] Cold temperatures disable the membrane ATPase, leading to higher results,[5] in winter months and when samples are subject to long collection runs to the laboratory.

In primary care, samples cannot be taken close to the point of analysis for rapid delivery without widespread routine use of point of care testing, which has its own difficulties. Laboratories could optimise carrying conditions and educate users: more systematic use of insulated specimen boxes in practices and temperature controlled transport systems in collection vans may help.

Problems in patients

Pathological conditions responsible for cellular potassium leakage are mostly haematological disorders identifiable on a blood count, notably thrombocytosis and pronounced leucocytosis.[6-9] This situation is not predictable, and warm storage of a sample with leucocytosis can produce the reverse effect, reducing the serum potassium as a result of intracellular potassium shift.[10] In vivo haemolysis should also be considered as a cause of raised potassium or repeated reports from the laboratory that samples are haemolysed, and can be investigated through a blood count, film, bilirubin measurement, reticulocyte count, and haptoglobin measurement. In some cases, potassium release on coagulation is exaggerated. This happens, for example, in hereditary or acquired stomatocytosis.[11]

In these situations an anticoagulated sample taken for analysis of plasma potassium will show a significantly higher than normal difference between the plasma and serum concentrations (typically about 0.3 mmol/l) than in the coagulated sample.

Box 2 | What should I do about raised serum potassium?

Identify patients at risk of having true rather than spurious hyperkalaemia or signs or symptoms of hyperkalaemia

- Patients with known chronic kidney disease
- Patients taking drugs that raise potassium (notably angiotensin converting enzyme inhibitors, angiotensin receptor blockers, potassium sparing diuretics, potassium salts) or laxatives (Movicol, Kleenprep Fybogel), trimethoprim, corticosteroids, βblockers, and non-steroidal anti-inflammatory agents, or using Lo salt
- Patients with obstructive uropathy
- Patients with clinical features such as myopathy, paralysis, arrhythmias, bradycardia
- Patients at greater risk from severe hyperkalaemia: those aged over 70 and those with serum urea >8.9 mmol/l
- Patients with acute illness (acute renal failure, ketoacidosis, etc)

Consider spurious hyperkalaemia in the absence of all the above

Box 3 | What should I do if I suspect raised serum potassium is spurious?

- Consider artefactual causes if patient has normal renal indices and serum bicarbonate, notably serum creatinine <100 µmol/l or estimated glomerular filtration rate >60 ml/min, and none of the factors listed in box 2 are present
- Consider causes:
  - Specimen was refrigerated or exposed to cold in transit
  - Long delay between venepuncture and separation
  - Difficult venepuncture with prolonged tourniquet time
  - In vitro (or occasionally in vivo) haemolysis
  - Patients with raised blood cell count (white cell count >15×109/l; platelets >700×109/l)
- Take action:
  - Take a second specimen to arrive at the laboratory within three hours of venepuncture
  - Remove tourniquet before drawing blood
  - Do not allow the specimen to cool below room temperature
  - Send simultaneous heparin specimen for potassium measurement
  - If recent blood count not available, send full blood count
  - If sequential samples are haemolysed, consider intravascular haemolysis
  - Consider electrocardiography in uncertain cases when potassium >6.0 mmol/l

Anticoagulation reduces the leakage of potassium that occurs on clotting and will produce a more physiological result. Lithium heparin is the recommended anticoagulant; plasma potassium EDTA (full blood count tube) should be avoided. Before the era of enclosed blood collection systems, pseudohyperkalaemia was commonly caused by blood or the needle being contaminated with the potassium rich anticoagulant. Potassium EDTA contamination still occurs and can produce large changes in serum potassium results.

The clearest indicators of probable spurious hyperkalaemia are clinical context and renal function. Hyperkalaemia is exceedingly rare in patients with normal renal function. It is exceptionally unlikely if renal indices are normal and there are no predisposing factors, notably a combination of potassium supplements and drugs that raise potassium, or a combination of potassium raising drugs.[12]

Pointers towards genuine hyperkalaemia are shown in box 2. Where (as in case 2) a bicarbonate result is available, a normal result further supports pseudohyperkalaemia, as in vivo hyperkalaemia is normally associated with metabolic acidosis. The patient's creatinine concentration and estimated glomerular filtration rate in case 2 had been stable over time and were consistent with mild (stage 3) chronic kidney disease, which is highly unlikely to raise serum potassium in the absence of other predisposing factors. Severe in vivo haemolysis or tissue breakdown (for example, rhabdomyolysis) can produce hyperkalaemia without renal dysfunction and cause true hyperkalaemia. In vivo haemolysis can be mistaken in the laboratory for in vitro haemolysis: discussion with the laboratory is recommended if samples are repeatedly reported as being haemolysed.

Improved guidance on the causes of pseudohyperkalaemia (box 3) may help to reduce the incidence of spurious results,[13] although these are unlikely to be completely avoidable. Access to point of care testing for a repeat test when required could avoid the distress of referring patients unnecessarily to emergency services.

A list of useful websites is given in the first article in this series.[14]

Evidence note

Most of the evidence relating to pseudohyperkalaemia comes from observational studies reporting the influence of ambient temperature or other conditions on serum and plasma potassium measurements, and from case reports or cohort studies examining the influence of blood dyscrasias on serum potassium. The guidance that true hyperkalaemia is rare in association with normal renal biochemistry is observational.

I thank Susan Richardson for typing this manuscript; A Taylor, who co-authored the answers in the original review; the clinical practice section of the Association of Clinical Biochemists (in particular I Bailey, J Davies, A Shenkin, A Hutchesson, Y Lolin) for commenting on this document, and D Housley (Association of Clinical Biochemists), R Gama, (Association of Clinical Pathologists), and N Campbell (Royal College of General Practitioners), who kindly reviewed the original authoring work and added valuable comments.

Competing interests: None declared.

1 Smellie WSA, Shaw N, Bowlees, R Taylor A, Howell-Jones R, McNulty CAM. Best practice in primary care pathology: review 9. *J Clin Pathol* 2007 Jan 26; doi: 10.1136/jcp.2006.044883.
2 Masters PW, Lawson N, Marenah CB, Maile LJ. High ambient temperature: a spurious cause of hypokalaemia. *BMJ* 1996;312:1652-3.
3 Seamark D, Backhouse S, Barber P, Hichens J, Salzmann M, Powell P. Transport and temperature effects on measurement of serum and plasma potassium. *J Roy Soc Med* 1999;92:339-41.
4 Verresen L, Lins RL, Neels H, De Broe ME. Effects of needle size and storage temperature on measurements of serum potassium. *Clin Chem* 1986;32:698-9.
5 Trull AK, Jackson C, Walsh S, Thornton A, Culank LS, McHugh J. The perennial problem with potassium. *Ann Clin Biochem* 2004;41(Pt 1):47-52.
6 Ingram RH, Seki M. Pseudohyperkalemia with thrombocytosis. *N Engl J Med* 1962;267:895-900.
7 Wulkan RW, Michiels JJ. Pseudohyperkalaemia in thrombocythaemia. *J Clin Chem Clin Biochem* 1990;28:489-91.
8 Colussi G, Cipriani D. Pseudohyperkalemia in extreme leukocytosis. *Am J Nephrol* 1995;15:450-2.
9 Thurlow V, Ozevlat H, Jones SA, Bailey IR. Establishing a practical blood platelet threshold to avoid reporting spurious potassium results due to thrombocytosis. *Ann Clin Biochem* 2005;42:196-9.
10 Adams PC, Woodhouse KW, Adela M. Parnham A. Exaggerated hypokalaemia in acute myeloid leukaemia. *BMJ* 1981;282:1034-5.
11 Stewart GW, Corrall RJ, Fyffe JA, Stockdill G, Strong JA. Familial pseudohyperkalaemia: a new syndrome. *Lancet* 1979;ii:175-7.
12 Mandal AK. Hypokalemia and hyperkalemia. *Med Clin North Am* 1997;81:611-39.
13 Johnston JD, Hawthorne SW. How to minimise factitious hyperkalaemia in blood samples from general practice. *BMJ* 1997;314:1200-1.
14 Smellie WSA. Testing pitfalls and summary of guidance in lipid management. *BMJ* 2006;333:83-6.

Accepted: 30 January 2007