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Persistent hyperkalaemia

Background
Persistent hyperkalaemia in elderly patients caused by hyporeninaemic hypoaldosteronism is relatively common and often under recognised in the general practice setting.

Objective
This article highlights the importance of suspecting hyporeninaemic hypoaldosteronism in any elderly patient with persistent hyperkalaemia and provides an outline of investigation and management of the condition.

Discussion
Elderly patients with persistent hyperkalaemia may have hyporeninaemic hypoaldosteronism. The diagnosis is made by calculating the transtubular potassium concentration gradient, and then measuring the serum aldosterone level. Hyporeninaemic hypoaldosteronism is managed with a low potassium diet and a low dose loop or thiazide diuretic.

Case study

Miss C, 87 years of age, was admitted for rehabilitation following split skin graft to bilateral calf wounds sustained from a fall. Miss C's comorbidities include hypertension, hyperthyroidism, osteoporosis and depression. She has some mild chronic renal impairment secondary to hypertension, with a baseline serum creatinine of 150 µmol/L (normal: 50–100 µmol/L). Her regular home medications include metoprolol, amlodipine, mirtazepine, vitamin D and carbimazole.

On examination, Miss C was clinically euvolaemic, with no evidence of heart failure. On the ward, Miss C's serum potassium was repeatedly found to be above 5.5 mmol/L (normal: 3.5–5.0 mmol/L), averaging 5.8 mmol/L with a peak of 6.4 mmol/L. She remained asymptomatic. Miss C was given 6 doses of oral resonium during the admission.

On further questioning, Miss C reported that she was first diagnosed as hyperkalaemic by her general practitioner after a routine blood test 3 years ago. She has maintained a low potassium diet since that time. Miss C had previously been referred by her GP to the emergency department of another hospital for hyperkalaemia; she was also found to be hyperkalaemic during an admission to another hospital. The actual cause of Miss C's hyperkalaemia, however, has not been investigated before the current hospital admission.

Serum potassium concentration is maintained by a relationship between potassium intake, the intracellular/extracellular distribution of potassium, and urinary potassium excretion. Persistent hyperkalaemia occurs when there is a defect in urinary potassium excretion.[1]

There are three major causes of chronic hyperkalaemia due to defective urinary potassium excretion:

- severe heart failure: this results in renal hypoperfusion, and consequently decreased sodium and water delivery to renal tubules, where potassium secretion occurs
- severe renal failure: this results in decreased renal secretion of potassium, and
- hypoaldosteronism.

The case study, Miss C, does not have heart failure. She does have chronic renal impairment, however the degree of her impairment does not fully account for the persistent hyperkalaemia. Therefore, hypoaldosteronism was suspected as a cause.

Aldosterone acts in the renal tubular cells to increase potassium secretion, and consequently urinary potassium excretion (*Figure 1*). The transtubular potassium concentration gradient (TTKG) is the potassium concentration gradient between urine at the end of the cortical collecting tubule and plasma.[2] It is calculated using the formula shown in *Figure 2*. It provides an estimate of the aldosterone activity and is useful in distinguishing hypoaldosteronism from other causes of persistent hyperkalaemia. A TTKG below 5 in a hyperkalaemic patient is highly suggestive of hypoaldosteronism.[2] Miss C's TTKG was 2.8. Hypoaldosteronism in Miss C was confirmed by an aldosterone level of <45 pmol/L (normal: 110–860 pmol/L).

What causes hypoaldosteronism?

Hypoaldosteronism can be caused by a number of things. Many commonly used drugs can interfere with the release or action of aldosterone (*Table 1*). Once drug interference is ruled out, other possible causes of hypoaldosteronism can include:

- hyporeninaemic hypoaldosteronism, and
- primary adrenal insufficiency.

Hyporeninaemic hypoaldosteronism is associated with low serum aldosterone and normal serum cortisol concentrations. In most, but

Figure 1. Aldosterone acts on renal tubular cell to increase sodium reabsorption and potassium secretion

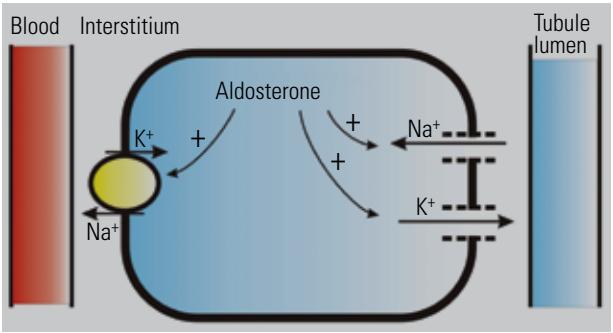

Figure 2. Calculation of the transtubular potassium concentration gradient (TTKG)

$$TTKG = \left(\left[\frac{\text{urine } K^+}{\left(\frac{\text{urine osmolality}}{\text{serum osmolality}} \right)} \right] \div \text{serum } K^+ \right)$$

not all cases, it is also associated with low plasma renin activity (PRA).[3] Primary adrenal insufficiency, on the other hand, is associated with low serum aldosterone, low serum cortisol concentrations and high PRA.[3] Hyponatremia can be an additional clue pointing to the possibility of primary adrenal insufficiency.

Miss C did not use any medication that interfered with the release or action of aldosterone,[4] so hyporeninaemic hypoaldosteronism was suspected. Miss C's PRA was 1.62 ng/mL/hour (normal: 0.6–2.8 ng/mL/hour) and her early morning cortisol was 572 nmol/L (normal: 120–620 nmol/L), thereby excluding primary adrenal insufficiency. Her HbA1c was 5.2% (normal: 4.0–6.0%), with a fasting glucose of 5.1 mmol/L (normal: 3.0–5.4 mmol/L), ruling out diabetes. Renal ultrasonography was unremarkable. Miss C was consequently diagnosed with hypoaldosteronism with normal PRA.

Hyporeninaemic hypoaldosternonism

Hyporeninaemic hypoaldosteronism is a syndrome in which there is decreased angiotensin II production, and consequently decreased aldosterone secretion.[3] It is associated with low PRA in most, but not all instances, as in the case of Miss C.[5] In this subset of patients with hyporeninaemic hypoaldosteronism, the main issue is decreased aldosterone secretion, which feeds back to stimulate renin secretion, causing a 'normal' PRA. Hypoaldosteronism causes decreased urinary potassium excretion, and thus hyperkalaemia.

Hyporeninaemic hypoaldosteronism is most common in elderly patients with mild to moderate renal impairment due to diabetic nephropathy or chronic interstitial nephritis.[3] The association between diabetic nephropathy and hyporeninaemic hypoaldosteronism is at least in part related to a problem in the conversion of prorenin to active renin in diabetic patients.[3]

Management

Hyporeninaemic hypoaldosteronism causing persistent hyperkalaemia needs to be treated in order to prevent it developing into potentially life threatening hyperkalaemia. Fludrocortisone has been shown to be an effective treatment,[3] unless, as in Miss C's case, the patient also has hypertension. Other measures include a low potassium diet and either a loop or thiazide diuretic.

Summary of important points

- Persistent hyperkalemia is usually associated with a problem in urinary potassium excretion.
- Hypoaldosteronism should be suspected in any patient with persistent hyperkalaemia who does not have severe renal and/or heart failure.
- TTKG is useful in distinguishing hypoaldosteronism from other causes of hyperkalamemia.
- Hyporeninaemic hypoaldosteronism is a common cause of persistent hyperkalaemia in elderly patients, especially those with diabetes.

Table 1. Drugs that interfere with the release or action of aldosterone[3]

Drug	Mechanism
• Nonsteroidal anti-inflammatory drugs (NSAIDs)	Inhibit prostaglandin synthesis, causing reduced renin secretion
• Angiotensin converting enzyme inhibitors (ACEIs)/angiotensin II receptor blockers (ARBs)	Inhibit angiotensin II production/action
• Potassium sparing diuretics: – spironolactone – eplerenone	Aldosterone antagonists
• Heparin	Causes toxicity in adrenal zona glomerulosa cells leading to decreased aldosterone secretion
• Trimethoprim • Trimethoprim-sulfamethoxazole	Closes sodium channels in luminal membrane of renal tubular cells

- Hyporeninaemic hypoaldosternonism usually causes hyperkalaemia if combined with other exacerbating factors, such as mild to moderate renal impairment and/or drugs.
- Hyporeninamic hypoaldosteronism can be managed with a low potassium diet and a loop or thiazide diuretic.

Case follow up

Miss C has been on a low potassium diet for the past 3 years and was given further dietary advice by a dietician during this hospital admission. A trial of frusemide 20 mg/day orally was successfully initiated to increase urinary potassium loss. (Due to renal impairment, she was unable to tolerate a higher dose.) As a result of these measures, Miss C's serum potassium has been maintained at 5.0 mmol/L.

Conflict of interest: none.

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