Teaching Point
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A woman with increasing weakness of the legs and irregular heartbeat who took her husband’s medication

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Case report

A 78-year-old woman presented to the emergency room complaining of a 2-week history of general fatigue and increasing weakness in both legs. She also experienced an irregular heartbeat and had slight dyspnea. She had had a cardiac syncope 1 year earlier and received a pacemaker (VVI mode). The woman reported a history of arterial hypertension and mild chronic heart failure. Because of previous intermittent tachyarrhythmia, she was treated with $2 \times 80$ mg sotalol and subcutaneously self-injected 0.3 ml nadroparin per day, a low-molecular weight heparin. She also received 10 mg enalapril, 0.07 mg digitoxin, $2 \times 0.2$ mg moxonidin, and 50 mg spironolactone per day. In addition to the prescribed medication, for approximately 2 months she had taking three to four effervescent tablets, originally prescribed for her husband, because she liked the refreshing taste of this sparkling preparation and felt that this was healthy. However, neither the patient nor her husband could recall the name of these tablets, but the husband promised to obtain the package.

Physical examination revealed dry mucous membranes without evidence of peripheral oedema. The heartbeat was irregular, a 2/6 systolic murmur was present over the right 2.ICR. Pulmonary auscultation was normal. Blood pressure was 170/90 mmHg. She had serious problems standing and there were signs of paralysis. Deep tendon reflexes were absent in both legs.

The admission electrocardiogram shows an arrhythmia interspersed with single pacemaker actions (Figure 1). In fact, the pacemaker saved the patient’s life because an immediately ordered serum potassium was 9.4 mmol/l. There was no evidence of pseudo-hyperkalaemia such as haemolysis, or blood count abnormalities, and venipuncture was without problems. Serum sodium was 138 mmol/l, calcium 2.60 mmol/l, and chloride 111 mmol/l. Creatinine was 1.3 mg/dl, BUN 39 mg/dl, and glucose 110 mg/dl. Venous blood gas analysis showed a pH 7.35, $P_{\text{CO}_2}$ 39.2 mmHg, and bicarbonate 21.1 mmol/l. Digitoxin was within the therapeutic concentration (14 µg/l).

Discussion

This is an illustrative case demonstrating how several pathophysiological factors worked together in inducing massive hyperkalaemia that was only survived because of the presence of a functioning pacemaker. Although it is generally assumed that typical electrographic findings of hyperkalaemia are tenting of T waves, followed by flattening of the P wave, and widening of QRS complexes, there is in fact a wide variability of electrocardiographic alterations in hyperkalaemia including atypical and minimal changes even in the presence of high potassium concentrations [1]. In this regard, the present electrocardiographic findings were not typical for the classical textbook findings of hyperkalaemia and likely represented the effects of other drugs influencing cardiac conduction including digitalis and sotalol.

The serum potassium concentration is determined by three factors: distribution of potassium between cells and extracellular fluid, dietary potassium intake, and potassium excretion into urine and faeces [2]. The majority of potassium (80–80%) is eliminated through the kidney. Potassium is freely filtered and is largely
reabsorbed (90%) by the time the tubular fluid reaches the collecting duct [2]. Renal regulation of potassium excretion largely depends on secretion and/or reabsorption at distal nephron sites such as distal convoluted tubules, and cortical and medullary collecting ducts. Principal cells secrete potassium whereas intercalated cells can reabsorb potassium during states of hypokalaemia [2].

Fig. 1. Electrocardiogram on admission. A pacemaker action is seen followed by a couplet of supraventricular premature complexes whereas the second supraventricular premature beat exhibits aberrant conduction.

Fig. 2. Schematic presentation of potassium regulation and potential impairment by the drugs prescribed. The principal cell is the main locus of renal potassium secretion. Aldosterone, after binding to its receptor, stimulates incorporation of sodium and potassium channels into the luminal membrane and also activates the sodium–potassium ATPase. Angiotensin II (ANG II) is a major stimulus for aldosterone synthesis and release in the adrenal gland. The ACE inhibitor enalapril as well as the non-selective β-receptor antagonist sotalol interfere with the generation of ANG II, thereby diminishing a major aldosterone stimulus. Aldosterone biosynthesis may be further impaired by low-molecular weight heparin and any remaining aldosterone reaching principal cells is blocked by spironolactone. Moreover, activity of the sodium–potassium ATPase, a necessary prerequisite for tubular potassium transport, is attenuated by digitalis even in therapeutic concentration. Finally, volume depletion and renal insufficiency impair tubular sodium delivery to the luminal sodium channels. If less sodium is taken up by principal cells a reduced potassium secretion results because of a diminished electrochemical gradient. Cellular uptake of potassium in extrarenal tissues also depends on active sodium–potassium ATPase that is inhibited by digitalis. Moreover, intracellular cAMP that is formed after β2-adrenoreceptor stimulation, activates sodium–potassium ATPase. Sotalol interferes with catecholamine-activated cellular potassium uptake and may further enhance hyperkalaemia by influencing transcellular shifts.
Aldosterone plays a pivotal role in excreting potassium by increasing the number of open sodium and potassium channels in the luminal membrane of principal cells (Figure 2). Moreover, aldosterone also enhances the activity of the sodium–potassium ATPase pump in the basolateral membrane. The first aldosterone-mediated event is an increase in sodium conductance that favours potassium secretion by making the lumen relatively electronegative.

ACE inhibitor treatment interferes with generation of angiotensin II and sotalol additionally antagonizes the β-adrenergic-induced release of renin at the macula densa. As a consequence, formation of a major stimulus for aldosterone synthesis and secretion, that is angiotensin II, is attenuated. In a recent study in 1818 patients using ACE inhibitors, hyperkalaemia developed in 11% [3]. Not surprisingly, impaired renal function, congestive heart failure, and long-acting ACE inhibitors were independently associated with the risk of hyperkalaemia in these patients [3]. Furthermore, it is well appreciated that heparin, including low-molecular weight heparins, suppresses aldosterone biosynthesis and can cause hyperkalaemia [4,5]. Finally, aldosterone actions were antagonized additionally by spironolactone in the present case. Thus, probably no aldosterone was active at the woman’s renal principal cells.

Reabsorption of luminal sodium is a necessary prerequisite for potassium secretion because the transport of sodium out of the cells by the sodium–potassium ATPase results in an increase in the intracellular potassium pool [6]. In addition, sodium reabsorption at the luminal membrane increases potassium secretion by depolarizing the membrane. Our patient exhibited severe volume depletion and mild renal insufficiency. It is possible that decreased distal nephron flow and a reduced luminal sodium delivery to the collecting duct may have further triggered hyperkalaemia because of a diminished electrochemical gradient for potassium secretion [5].

Severe digitalis poisoning, that was not present in our case, results in overt hyperkalaemia by impeding potassium entry into cells through inhibition of sodium–potassium ATPase (Figure 2). This may occur in principal cells where the aldosterone-stimulated activity of the sodium–potassium ATPase is essential for potassium secretion as well as in extrarenal sites. However, there is also evidence that already therapeutic concentrations of glycosides may result in mild extracellular elevation of potassium [6].

Sotalol is a competitive, non-specific β-adrenoceptor blocker that also prolongs duration of action potentials. Like all non-selective β-adrenoreceptor blockers, sotalol interferes with β2-adrenergic-mediated potassium uptake by cells (Figure 2). Although this effect is normally associated with only a minor elevation in potassium concentration because the extracellular potassium excess can be easily excreted in the urine, β-adrenergic blockade may become relevant in situations such as in patients with an increased potassium load, renal insufficiency, and defects in potassium handling (hypoadosteronism).

The normal kidney can excrete several hundred milliequivalent potassium per day [5,7]. However, if renal potassium excretion is impaired through renal insufficiency, excess intake produces hyperkalaemia. In fact, some studies estimate that in 50% of clinical cases of hyperkalaemia, potassium supplements play

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**Fig. 3.** Electrocardiogram after efficacious treatment of hyperkalaemia. Sinus rhythm is present with no pacemaker spikes, and ST-segment depressions are likely due to digitalis.
a role [2]. The woman took three to four effervescent potassium tablets, each containing 40 mmol. It is probable that this additional daily potassium intake contributed to the life-threatening hyperkalaemia in the presence of impaired renal excretion and inhibited cellular uptake of potassium in other tissues.

Although infusion of calcium is the treatment of choice for patients with hyperkalaemia and significant electrocardiographic abnormalities [2], it was felt that it may increase digitalis toxicity and was therefore not given. The patient received insulin and glucose (50 ml 50% glucose with 10 U insulin followed by 5% glucose infusion), and 5 mg of the β2-adrenergic agonist salbutamol in saline by nasal inhalation. She was rehydrated with 2 l of 0.9% saline and also received 60 mg furosemide intravenously. Finally, she was given an oral dose of 20 g sodium polystyrene sulfonate. Enalapril, spironolactone, and digitoxin were discontinued. Two hours after initiating this treatment, the serum potassium had already decreased to 7.6 mmol/l, and was 5.1 mmol/l after 12 h. The electrocardiogram at that time point (Figure 3) showed sinus rhythm with no pacemaker spikes, and curved ST-segment depressions, probably due to digitalis. The woman was instructed to refrain from taking her husband’s potassium preparations.

### Teaching points

- Several drugs will interfere with the complex mechanisms of potassium homeostasis.
- Electrocardiographic findings in hyperkalaemia are not always tenting T waves.
- Do not take the medications of your spouse. Take only the drugs prescribed for yourself.

### References