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Iatrogenic hyperkalaemia—points to consider in diagnosis and management

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Introduction

Hyperkalaemia is a potentially life-threatening electrolyte abnormality. In normal subjects it is rare because the homeostatic mechanisms to maintain normokalaemia are highly effective. In particular, the capacity of renal potassium excretion is very high under normal circumstances [1–4]. Consequently, hyperkalaemia is practically always associated with impaired urinary potassium excretion [5], but in patients with acute or chronic renal failure high potassium intake can further contribute to the development of hyperkalaemia (Table 1).

We describe three cases of iatrogenic hyperkalaemia secondary to drug therapy. The cases illustrate the wide spectrum of causes and preconditioning circumstances. Based on these cases we discuss the appropriate clinical management of this problem.

Case report 1

A 71-year-old man was admitted to our hospital for evaluation of hyperkalaemia (serum potassium 6.1 mmol/l) and renal impairment (serum creatinine 160 μmol/l, creatinine clearance 60 ml/min). Laboratory investigation established the diagnosis of hyporeninaemic hypoaldosteronism secondary to chronic interstitial nephritis of unknown origin. A low-potassium diet plus small doses of frusemide were introduced and the patient was discharged. A few days later he developed a urinary tract infection due to *E coli* and co-trimoxazole in conventional doses (1600 mg of sulphamethoxazole + 320 mg of trimethoprim) was administered. Five days later the patient was referred to our hospital with profound muscle weakness, nausea, and constipation. Laboratory investigation on the patient's admission showed severe hyperkalaemia (serum potassium 7.8 mmol/l) with ECG changes (peaked narrow T waves and a shortened QT interval). Hyperkalaemia was accompanied by low potassium excretion (urine potassium 19 mmol/l, FE_{K+} 9%, TTKG 2.4). Additionally, a normal anion gap hyperchloraemic metabolic acidosis with an arterial pH of 7.29, a pCO_2 of 32 mmHg, a serum chloride level of 112 mmol/l, a serum bicarbonate of 15 mmol/l, a urine anion gap of 23 mmol/l, and a urine pH of 5.1 was found. There was also evidence of a low urea excretion (FE_{urea} 7.2%) in the face of the serum urea levels (6.6 mmol/l). Co-trimoxazole was discontinued and hyperkalaemia was appropriately treated. Serum potassium levels were then stabilized at 5.5–6 mmol/l.

Table 1. Causes of hyperkalaemia

1. *Increased (oral/intravenous) potassium intake*
2. *Increased potassium release from cells*
Pseudohyperkalaemia
Metabolic acidosis
Insulin deficiency, hyperglycaemia and hyperosmolality
β-Adrenergic blockers
Increased tissue catabolism
Severe exercise
Hyperkalaemic periodic paralysis
Drugs: digitalis overdose, succinylcholine, arginine
3. *Reduced urinary potassium excretion*
Renal failure
Effective circulating volume depletion
Selective impairment of potassium excretion
Hypoaldosteronism

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Case report 2

A 73-year-old woman with a history of hypertension, non-insulin-dependent diabetes mellitus and hyperlipidaemia was admitted because of malaise, diffuse muscle pain and marked weakness. She had been given quinapril, amlodipine, gliclazide, and long-acting bezafibrate. On physical examination all muscle groups were extremely tender and she could not raise her limbs. Laboratory investigation on patient's admission were as follows: haematocrit 34%, white blood cell count 8000/μl, platelet count 200 000/μl, serum glucose 19.9 mmol/l, creatinine 186 μmol/l, urea 42.5 mmol/l, potassium 6.5 mmol/l, uric acid 512 μmol/l, sodium 140 mmol/l, chloride 100 mmol/l, SGOT 860 IU

(normal values 5–40 IU/l), SGPT 335 IU/l (normal values 5–40 IU/l), CK 22 000 IU/l (normal values 40–190 IU/l), LDH 4280 IU (normal values 225–450 IU/l), and aldolase 730 IU (normal values 0–8 IU/l). Arterial blood gases showed pH 7.31, pCO_2 34.5 mmHg, and bicarbonate 16 mmol/l. The serum anion gap was 24 mmol/l. The patient's urine was brown, cloudy, and strongly positive for blood. The urinalysis contained scarce granular casts, 14–20 white cells and 15–20 red cells per high-power field. Fibrate was discontinued, hyperkalaemia was properly treated, and vigorous intravenous fluid therapy to correct the hypovolaemia was administered. Treatment was followed by a progressive decrease in serum creatinine, potassium and muscle enzymes towards normal values. On the patient's discharge 10 days later, muscle enzymes were normal, serum potassium was 4.5 mmol/l, serum creatinine 132 μmol/l, and creatinine clearance was 60 ml/min.

Case report 3

A 74-year-old patient was referred to our hospital with acute weakness, fatigue, flatulence and vomiting. He was hypertensive and was receiving quinapril 20 mg once daily and a combination of frusemide plus amiloride (40 mg + 5 mg) once daily. A mild impairment in renal function had been diagnosed (serum creatinine 160 μmol/l) 3 years before, as well as osteoporosis for which he was administered vitamin D and calcium. Laboratory investigation on patient's admission revealed urea 71.4 mmol/l, creatinine 336 μmol/l, glucose 9.2 mmol/l, sodium 130 mmol/l, potassium 8.2 mmol/l, calcium 2.7 mmol/l, phosphorus 1.94 mmol/l, magnesium 0.9 mmol/l, chloride 106 mmol/l, bicarbonate 12 mmol/l, anion gap 12 mmol/l, arterial pH 7.30, and pCO_2 25 mmHg. Creatinine clearance was 20 ml/min. Urinalysis showed that the urine sediment contained 18–20 red cells and 5–6 white cells per high-power field. Urine pH was 5.5. There were ECG changes suggestive of hyperkalaemia (peaked narrow T waves and a shortened QT interval). Both kidneys were of small size with increased echogenicity by ultrasonic examination. Antihypertensive drugs were discontinued. Two haemodialysis sessions were carried out and the hyperkalaemia was corrected. A progressive clinical and laboratory improvement was achieved and he was discharged 5 days later when laboratory evaluation revealed urea 24 mmol/l, creatinine 168 μmol/l, potassium 4.8 mmol/l, sodium 146 mmol/l, calcium 2.37 mmol/l, and arterial pH 7.35. A calcium-channel blocker was then given for blood pressure control.

Discussion

These cases illustrate the wide spectrum of causes and clinical manifestations of drug-induced hyperkalaemia. The incidence of this electrolyte abnormality has been increasing in recent years. In practically all patients with sustained elevation of serum potassium concentration predisposing conditions can be found, which interfere with potassium homeostasis and especially with renal potassium excretion. Examples include renal insufficiency (even of mild degree) or hypoaldosteronism (Table 2) and this is also illustrated by our patients [6–8]. It is of interest that typically the patients were elderly: In elderly subjects age-specific changes of renal function increase the risk of hyperkalaemia, particularly when other potassium-regulatory systems have been compromised [7,9–12].

The first case illustrates that conventional doses of trimethoprim may cause hyperkalaemia when additional predisposing conditions are present, i.e. in this case advanced age with hyporeninaemic hypoaldosteronism [13–16]. Trimethoprim inhibits amiloride-sensitive sodium channels in the distal nephron and dose-dependently reduces the transepithelial voltage which facilitates potassium secretion [17,18]. It has been reported that even low doses of trimethoprim can significantly decrease net transepithelial sodium transport and thus lower potassium excretion [18]. In so-called renal tubular acidosis type IV, associated with hyporeninaemic hypoaldosteronism and hyperkalaemia, tubular pH is typically low. This increases the concentration of the charged protonated species of trimethoprim, which blocks epithelial sodium channels most effectively. Thus, the antikaliuretic effect of trimethoprim is further increased [19]. Finally, nausea, as in our patient, reduces protein intake; low urea excretion (as documented by a low FE_{urea}) could have led to a low flow rate and delivery of tubular fluid to the cortical collecting duct. This may have further contributed to a lower rate of potassium excretion in our patient and may have further exacerbated the impact of trimethoprim-mediated blockage of sodium channels

Table 2. Causes of hypoaldosteronism

Associated with decreased activity of the renin–angiotensin system and low aldosterone levels
Hyporeninaemic hypoaldosteronism (diabetes mellitus most common)
Non-steroidal anti-inflammatory drugs (with possible exception of sulindac)
Angiotensin converting enzyme inhibitors
Cyclosporin
Acquired immunodeficiency syndrome
Reduced adrenal synthesis
(a) low cortisol levels: primary adrenal insufficiency, congenital adrenal hyperplasia (primarily 21-hydroxylate deficiency)
(b) normal cortisol levels: heparin, post-removal of adrenal adenoma, isolated hypoaldosteronism (in cases of severe illness)
Aldosterone resistance with normal or increased aldosterone levels
Potassium-sparing diuretics
Trimethoprim
Cyclosporin
Pseudohypoaldosteronism (hereditary or acquired resistance to aldosterone)

Table 3. Drug-induced rhabdomyolysis

Antibiotics	: isoniazid, co-trimoxazole
Antifungal drugs	: amphotericin B
Antiparasitic drugs	: pentamidine
Analgesics	: opiates
Antidepressants	: tricyclic antidepressants, MAO inhibitors
Antiepileptics	: valproic acid
Psychiatric drugs	: phenothiazines, butyrophenones
Antihistamines	
Sedative–hypnotic drugs	: benzodiazepines, barbiturates
Hypolipidaemic drugs	: fibrates, statins
Hormones	: vasopressin
Vitamins	: retinoids
Drug causing hypokalaemia	: diuretics, emetin, laxatives
Asthma preparations	: theophylline, terbutaline
Antifibrinolytic drugs	: E-aminocaproic acid
Fibrinolytic drugs	: streptokinase
Other drugs	: alcohol, amphetamines, cocaine, caffeine, colchicine, LSD, simetidine

on potassium excretion [20]. As to the management of such patients, it should be mentioned, that the antikaliuretic effects of trimethoprim are minimized by raising urine pH [19], as well as by manoeuvres that increase distal delivery of sodium, e.g. administration of frusemide and of saline [21].

Drug-induced hyperkalaemia can also be caused by drug-induced rhabdomyolysis, as illustrated by the second patient. Table 3 summarizes that, especially in the elderly patient [22,23], a number of drugs, alone or in combination, can cause muscle damage, deterioration of renal function, and hyperkalaemia. Under normal circumstances, the renal tubular cell will respond to an increase in serum potassium concentration by augmenting potassium secretion. If tissue destruction is intense, the ability of the kidney to excrete the potassium may be overwhelmed, so that hyperkalaemia ensues [24,25]. The risk is further aggravated, if rhabdomyolysis-induced renal failure occurs. In this circumstance, hyperkalaemia may became life threatening. In our case, administration of ACE inhibitors and the resulting relative hypoaldosteronism, may have also interfered with potassium excretion [26,27], illustrating that not infrequently several predisposing factors can be found in such complex situations. Hypolipidaemic drugs, e.g. fibrates and statins, may cause myolysis [28–30], specifically when long-acting bezafibrate preparations are administered to elderly patients with reduced renal function without appropriate modification of the dose of the drug [24,29,31,32]. Our case illustrates the necessity, particularly in the elderly patient, of adjusting the dose to the renal function and to monitor CK levels as the first sign of impending muscle damage [24].

The third case illustrates that simultaneous administration of drugs with known hyperkalaemic potential may cause a dangerous increase in serum potassium concentration, again particularly in elderly patients with even minor reduction in renal function [6–8]. ACE inhibitors reduce conversion of angiotensin I to angiotensin II in the circulation and perhaps also in the adrenal zona glomerulosa [33], and decrease both angiotensin II and potassium-mediated aldosterone release [33,34]. In patients with normal renal function, serum potassium rarely increases by more than 0.5 mmol/l [35]. In patients with diminished renal function, as in our patient, the rise in potassium concentration may be more marked, since the increment is inversely related to GFR [26], particularly in patients with hyporeninaemic hypoaldosteronism (e.g. in diabetic nephropathy), in patients on beta-adrenergic blockers or in patients with potassium-sparing diuretics, as in our case [6,26,27,36–38]. The combination of potassium-sparing diuretics and ACE inhibitors should be avoided and the effects of potassium supplements on serum potassium concentrations must be closely monitored in elderly patients on ACE inhibitors [8,10,12,26,27].

Table 4 summarizes the great number of drugs with reports on drug-induced hyperkalaemia.

Beta-adrenergic antagonists may cause hyperkalaemia following a potassium load, severe exercise, or in the presence of hypoaldosteronism or renal failure [39–42]. They alter transcellular partitioning of potassium and reduce the activity of the renin–aldosterone system [5,39]. Central adrenergic inhibitors, e.g. clonidine, or beta-1-selective blockers, e.g. atenolol, interfere less with potassium homeostasis [43–45]. Non-steroidal anti-inflammatory drugs lower plasma renin. As a consequence, plasma potassium concentration rises moderately, by approximately 0.2 mmol/l in subjects with normal renal function, but may rise by more than 1 mmol/l when renal function is impaired or when potassium homeostasis is strained, e.g. administration of potassium-sparing diuretics or non-cardioselective beta blockers [46–48]. Prolonged heparin administration may cause hyperkalaemia *via* inhibition of adrenal 18-hydroxylase [49–53]; the risk of hyperkalaemia is exacerbated by administration of ACE inhibitors or presence of long-standing diabetes mellitus [49,52–55]. An interesting condition, recently reported, is selective

Table 4. Mechanisms of drug-induced hyperkalaemia

1. *Increased potassium release from cells*
   - β-Adrenergic blockers
   - α-Adrenergic agonists
   - Insulin antagonists (somatostatin, diazoxide)
   - Arginine hydrochloride
   - Succinylcholine
   - Digitalis
2. *Decreased activity of the renin–angiotensin axis*
   - Angiotensin converting enzyme inhibitors
   - β-Adrenergic blockers
   - Non-steroidal anti-inflammatory drugs
   - Heparin
3. *Inhibition of potassium secretion*
   - Spironolactone
   - Amiloride
   - Trimethoprim
   - Triamterene
   - Pentamidine
   - Cyclosporin A

hypoaldosteronism in critically hypoxic patients which predisposes to heparin-induced hyperkalaemia [12,56]. Hyperkalaemia may also occur with low-molecular-weight heparin preparations [57,58]. Severe hyperkalaemia has been reported after prolonged use of pentamidine to treat HIV-associated *Pneumocystis carinii*. Like trimethoprim, pentamidine acts in the cortical collecting tubule to decrease the electrochemical driving force for potassium and hydrogen secretion [59]. Patients with HIV or AIDS who receive pentamidine or high doses of trimethoprim are at particular risk of hyperkalaemia [12,17,59]. This risk is further aggravated by the frequent occurence of adrenalitis, presumably of infectious origin, e.g. cytomegalovirus or mycoplasma avium intracellulare [60].

Cyclosporin A may cause hyperkalaemia by inhibiting Na^+–K^+–ATPase activity, leading to diminished potassium accumulation and transepithelial potential in potassium-secreting tubular cells, thus diminishing the driving force for potassium secretion [61]. A role of vasoconstriction and reduced GFR on the one hand and mineralocorticoid resistance on the other has also been postulated [12,62].

Digitalis dose dependently inhibits Na^+–K^+–ATPase. Toxic doses, e.g. ingested in a suicide attempt, may cause hyperkalaemia [63–66].

It is obvious from the above that the physician in charge of a patient with hyperkalaemia has to assess renal function and drug history of the patient carefully.

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