Drug Saf (2014) 37:677–692
DOI 10.1007/s40264-014-0196-1

REVIEW ARTICLE

Drug-Induced Hyperkalemia

Chaker Ben Salem · Atef Badreddine · Neila Fathallah · Raoudha Slim · Houssem Hmouda

Published online: 22 July 2014

Abstract Hyperkalemia is a common clinical condition that can be defined as a serum potassium concentration exceeding 5.0 mmol/L. Drug-induced hyperkalemia is the most important cause of increased potassium levels in everyday clinical practice. Drug-induced hyperkalemia may be asymptomatic. However, it may be dramatic and life threatening, posing diagnostic and management problems. A wide range of drugs can cause hyperkalemia by a variety of mechanisms. Drugs can interfere with potassium homoeostasis either by promoting transcellular potassium shift or by impairing renal potassium excretion. Drugs may also increase potassium supply. The reduction in renal potassium excretion due to inhibition of the renin-angiotensin-aldosterone system represents the most important mechanism by which drugs are known to cause hyperkalemia. Medications that alter transmembrane potassium movement include amino acids, beta-blockers, calcium channel blockers, suxamethonium, and mannitol. Drugs that impair renal potassium excretion are mainly represented by angiotensin-converting enzyme inhibitors, angiotensin-II receptor blockers, direct renin inhibitors, nonsteroidal anti-inflammatory drugs, calcineurin inhibitors, heparin and derivatives, aldosterone antagonists, potassium-sparing diuretics, trimethoprim, and pentamidine. Potassium-containing agents represent another group of medications causing hyperkalemia. Increased awareness of drugs that can induce hyperkalemia, and monitoring and prevention are key elements for reducing the number of hospital admissions, morbidity, and mortality related to drug-induced hyperkalemia.

Key Points

Drug-induced hyperkalemia is the most important cause of increased potassium levels in everyday clinical practice.

A wide range of drugs can cause hyperkalemia by a variety of mechanisms.

Increased awareness of drugs that can induce hyperkalemia, and monitoring and prevention are key elements for reducing the number of hospital admissions, morbidity, and mortality related to drug-induced hyperkalemia.

1 Introduction

Hyperkalemia is a common clinical condition defined as a serum potassium concentration exceeding 5.0 mmol/L. In hospitalized patients, the incidence of hyperkalemia ranges from 1.3 to 10 %, with a mortality rate of 1 per 1,000 patients [1, 2]. Drug-induced hyperkalemia is the most important cause of increased serum potassium in everyday clinical practice [3, 4]. Drugs have been identified as a primary cause or contributing factor of hyperkalemia in 35–75 % of hospitalized patients [3]. Drug surveillance studies have reported the development of clinically significant hyperkalemia in up to 10 % of patients receiving

C. Ben Salem (✉) · A. Badreddine · N. Fathallah · R. Slim
Department of Clinical Pharmacology, Faculty of Medicine of Sousse, Farhat Hached University Hospital, Avenue Mohamed Karoui, 4002 Sousse, Tunisia
e-mail: bensalem.c@gmail.com

H. Hmouda
Medical Intensive Care Unit, Sahloul University Hospital, Sousse, Tunisia

Table 1 List of drugs known to cause hyperkalemia

Medication	Mechanism
Drug-inducing transmembrane potassium movement	
β blockers	Decrease activity of Na^+/K^+-ATPase pump and renin release
Digoxin intoxication	Inhibition of Na^+/K^+-ATPase pump activity
Intravenous cationic amino acids	Increase in extracellular potassium shifts
Mannitol	Hyperosmolality with increase of extracellular potassium shifts
Suxamethonium	Prolonged depolarization of cell membrane
Verapamil	Blockade of calcium channels
Drugs that affect aldosterone secretion	
ACE inhibitors	Blockade of angiotensin II synthesis with decrease of aldosterone secretion. Impaired delivery of sodium to the distal nephron
ARBs	Competitive binding to the angiotensin II receptor with decrease of aldosterone synthesis
Direct renin inhibitors	Inhibition of the conversion of angiotensinogen to angiotensin I with decease of aldosterone formation
NSAIDs	Decrease of prostaglandin-mediated renin release, renal blood flow and glomerular filtration rate
Calcineurin inhibitors	Decrease aldosterone synthesis and Na^+/K^+-ATPase pump activity
Drug that cause tubular resistance to the action of aldosterone	
Aldosterone antagonists	Blockade of mineralocorticoid receptors
Potassium-sparing diuretics	Blockade of luminal sodium channels
Trimethoprim, pentamidine	Blockade of luminal sodium channels
Potassium-containing agents	
Salt substitutes and salt alternatives	Increase in potassium supply
penicillin G, stored blood products	

ACE angiotensin-converting enzyme, *ARBs* angiotensin II receptor blockers, *ATPase* adenosine triphosphatase, *NSAIDs* nonsteroidal anti-inflammatory drugs

culprit medications [5]. In a retrospective observational study of 168 non-dialyzed patients who presented with a serum potassium value of at least 6.5 mmol/L at admission or during hospital stay, more than 60 % of cases were taking at least one drug known to cause or worsen hyperkalemia [6]; 10 % of deaths in this study were potentially attributed to drug-associated hyperkalemia.

A wide range of drugs can cause hyperkalemia by a variety of mechanisms (Table 1). Drugs can interfere with potassium homoeostasis either by promoting transcellular potassium shift or by impairing renal potassium excretion. Drugs may also increase potassium supply. High-risk patients are those with predisposing conditions, such as moderate-to-severe chronic renal insufficiency or hypoaldosteronism, the elderly, and those taking combinations of medications known to cause a rise in serum potassium concentrations.

Drug-induced hyperkalemia may be asymptomatic. However, it may be dramatic and life threatening, posing diagnostic and management problems. When symptoms are present, they are non-specific and predominantly related to cardiac function or muscular function. Manifestations of hyperkalemia include diarrhea, abdominal pain, paresthesia, muscle weakness, ascending paralysis, and respiratory failure. Some cases of hyperkalemia can be misleading, with a clinical picture highly suggestive of Guillain-Barré syndrome. Hyperkalemia causes abnormalities in cardiac conduction, which result in diagnostic alterations in the electrocardiogram. They include peaked T waves, prolongation of the PR interval, and QRS widening followed by loss of atrial activity, ventricular fibrillation, and asystole.

Recognition of medications known to cause hyperkalemia and the mechanisms by which they impair potassium homeostasis is crucial for adequate management. A careful drug history is essential in patients with this electrolyte abnormality.

In this review article, we describe some of the common drugs known to induce hyperkalemia, and their underlying mechanisms and clinical significance. Although drugs producing rhabdomyolysis, renal failure, or tumor lysis may cause hyperkalemia, they are not included in our review. Herbal remedies are also excluded from this review.

Data were identified from MEDLINE and SCOPUS from January 1960 to December 2013, and from Reactions Weekly from 1992 to December 2013, regardless of the language. We used the keywords 'hyperkalemia' and

'potassium disorders' with the subheading 'drug-induced', 'drug-associated'. Certain drugs were directly inserted as keywords, such as 'aldosterone antagonists', 'angiotensin-converting enzyme inhibitors' and 'angiotensin-II receptor antagonists'. Searches also included the terms 'blood' and 'potassium/drug effects'. If we found relevant articles in many languages that described the same topic, only English articles were analyzed. Identified articles were evaluated to determine whether any of their references contained additional relevant publications. Information from reviews focusing on this topic has also been considered [3, 4]. We excluded articles with insufficient clinical or laboratory data.

2 Causative Drugs

2.1 Medications that Alter Transmembrane Potassium Movement

Several drugs can affect transfer of potassium between the extracellular and intracellular fluid to increase the concentration in serum.

2.1.1 Amino Acids

Intravenous administration of natural (lysine, arginine) and synthetic (epsilon-aminocaproic acid) cationic amino acids has been shown to induce hyperkalemia in both human and animal studies. Epsilon-aminocaproic acid, lysine, and arginine have a structural similarity, which explains the mechanism of hyperkalemia. Cationic amino acids induce movement of potassium from the intracellular to extracellular space to preserve the electroneutrality [7]. Animal studies have shown that infusion of amino acids such as lysine and arginine induce hyperkalemia related to skeletal muscle uptake of amino acids and release of an equivalent opposite charge of intracellular potassium. Barone et al. [8] studied the effect of different amino acid solutions on a variety of chemical parameters. They noticed a significant increase of serum potassium at 2.5 h post-infusion during 50 g lysine or 25 g lysine/25 g arginine. The individual values of serum potassium were in excess of 5 mmol/L in 10 of 12 patients (maximum value 6.2 mmol/L). Giovacchini et al. [9] evaluated the frequency and the magnitude of hyperkalemia after an infusion of a solution containing 25 g of arginine hydrochloride and 25 g of lysine hydrochloride in neuroendocrine tumor patients undergoing targeted radiopeptide therapy. They found that, at 4 h after the beginning of the amino acid infusion, 24 of the 31 patients (77 %) had K^+ levels above the normal range, and six (19 %) showed severe hyperkalemia ($K^+ \geq 6$ mmol/L). The highest potassium level was 6.7 mmol/L. At 24 h, only four patients (13 %) had potassium serum levels above the normal range. Although the increase of serum potassium level by lysine and arginine is moderate and transitory, severe hyperkalemia (potassium levels >7 mmol/L) may be observed in patients with moderate renal insufficiency or severe hepatic disease as a result of an inability to excrete the large potassium load in renal dysfunction, and inability to metabolize the arginine in liver disease [10, 11].

Epsilon-aminocaproic acid, a derivative and analog of the amino acid lysine used to treat excessive postoperative bleeding, may induce life-threatening hyperkalemia, particularly in patients with reduced renal function [7, 12]. Hyperkalemia is usually prevented by urinary excretion of the potassium liberated from muscle. However, in renal dysfunction, epsilon aminocaproic acid accumulates in the extracellular fluid and causes transcellular shift of potassium, which in turn cannot be excreted. Furthermore, if liver function is also impaired, all the administered epsilon aminocaproic acid is available for uptake by muscle, and serum potassium concentration rises maximally [13].

2.1.2 Beta-Blockers

Moderate increases in serum potassium concentrations as low as 0.3 mmol/L subsequent to beta-blocker therapy have been observed in several controlled clinical trials [11, 14]. However, beta-blocker therapy can increase serum potassium values by 1 mmol/L or more in end-stage renal disease, and in patients undergoing cardiopulmonary bypass procedures [15, 16]. Furthermore, in some cases, hyperkalemia was severe enough to make removal from bypass circulation difficult.

Hyperkalemia was mainly seen with nonselective rather than with cardio-selective beta-blockers. Nonselective beta-blockers have been associated with contributing factors to hyperkalemia, such as other medications and/or coexistent renal disease, in 4–17 % of hospitalized patients [3]. Severe hyperkalemia as a complication of timolol, a topically applied beta-blocker has also been reported [17]. Beta-blockers can confer a predisposition to the development of hyperkalemia through two potential mechanisms. These drugs can interfere with the cellular uptake of potassium through decreased activity of a sodium potassium pump (Na^+/K^+-adenosine triphosphatase [ATPase]) [18]. In addition, they block the stimulatory effect of the sympathetic nervous system on the release of renin [19]. Hyperkalemia occurring within hours after intravenous administration of labetalol implies that impaired cellular uptake of potassium, rather than decreased aldosterone synthesis, is the main mechanism [20].

The duration of this hyperkalemia can be fairly prolonged in patients with advanced chronic kidney disease (CKD), particularly when renally cleared beta-blockers, such as atenolol, are administered [15].

2.1.3 Calcium Channel Blockers

The implication of calcium channel blockers in the pathogenesis of dyskalemia remains uncertain [21]. Hyperkalemia has been rarely reported with calcium channel blockers such as verapamil, diltiazem, amlodipine, and benidipine [22, 23]. However, the etiology of hyperkalemia seems to be multifactorial in these cases. In fact, CKD, hypoaldosteronism, and other concomitant hyperkalemia-inducing drugs are usually present.

The majority of the cases of hyperkalemia associated with calcium channel blockers have been reported with verapamil. This drug may decrease potassium movement from the extracellular to the intracellular space by blocking calcium channels [23]. It seems to block aldosterone production. In addition, its chronic administration may attenuate aldosterone responsiveness to angiotensin II [24]. It is also postulated that verapamil-associated hyperkalemia is a result of diminished renal function after an adverse hemodynamic effect on ventricular function [23].

2.1.4 Suxamethonium

Suxamethonium (also known as succinylcholine), the only depolarizing neuromuscular blocker in clinical use, is known to cause hyperkalemia by causing an extracellular shift of potassium [25]. The resulting hyperkalemia relates to extra-junctional acetylcholine receptors spread across the muscle membrane that undergo prolonged depolarization in response to succinylcholine, with release of potassium [26]. Succinylcholine-induced hyperkalemia is dose dependent. It causes an increase in serum potassium up to 1 mmol/L, which peaks in 2–5 min and then lasts less than 10–15 min [27]. However, in some instances, the reversal to normokalemia may take much longer [25]. Marked hyperkalemia has been reported in patients with burns, occult myopathies, trauma, and severe infection. These clinical conditions per se lead to hyperkalemia.

2.1.5 Digoxin

Hyperkalemia can result from both acute and chronic digoxin toxicity with associated fatality [28, 29]. However, therapeutic digoxin levels do not lead to hyperkalemia unless there are other predisposing factors for impaired potassium handling. Indeed, potentially lethal hyperkalemia can occur in hemodialysis patients who ingest therapeutic quantities of digoxin [30]. The combination of hyperkalemia and bradycardia strongly predicted fatality even in cases with appropriate digoxin immune fragment antigen-binding (Fab) administration. The mechanism of digoxin-associated hyperkalemia seems to be due to impaired cellular uptake of potassium by inhibition in dependent dose manner of Na^+/K^+-ATPase activity [4].

2.1.6 Mannitol

Mannitol, used in the treatment of cerebral edema and raised intra-ocular pressure, can cause hyperkalemia with high doses (2 g/kg) [31, 32]. Serum potassium increases by 0.4–0.8 mmol/L for every 10 mOsm/kg increase in the effective plasma osmolality. The peak potassium concentrations were noted within 1–2 h after completion of mannitol. Possible mechanisms include expansion of extracellular fluid volume leading to bicarbonate dilution and hence dilutional acidosis, hemolysis due to red blood cell crenation by mannitol, and shift of intracellular potassium to the extracellular space due to hyperosmolality caused by mannitol [33]. The rise in potassium may not be dependent on pH changes, and hyperkalemia may occur with or without metabolic acidosis [34]. Mannitol-induced hyperkalemia may be severe, with adverse effects on cardiac rhythm.

2.2 Medications that Impair Renal Potassium Excretion

Reduction in renal potassium excretion due to inhibition of the renin–angiotensin–aldosterone system (RAAS) is the most important mechanism by which drugs are known to cause hyperkalemia. Renin, secreted by the juxtaglomerular cells in the afferent arteriole, acts on angiotensinogen to form angiotensin I. Angiotensin I is converted to angiotensin II by angiotensin-converting enzymes (ACEs). Angiotensin II stimulates the release of aldosterone from the zona glomerulosa cells in the adrenal gland.

Aldosterone, secreted by the zona glomerulosa of the adrenal glands, is bound to its nuclear mineralocorticoid receptor (MR) in the distal tubule and the principal cells in the cortical collecting duct (CCD), colon, and sweat glands and increases K^+ excretion [35]. It activates the basolateral Na^+/K^+-ATPase and therefore increases intracellular potassium concentration and enhances potassium secretion to the lumen. In addition, aldosterone stimulates the expression of the epithelial sodium channels (ENaC), increasing the likelihood of this channel to be open to the luminal side, and thus increases the electrochemical driving force for potassium excretion [36]. Angiotensin II also directly stimulates ENaC in the CCD via type 1 angiotensin II receptors.

Aldosterone also increases renal outer medullary potassium (ROMK) channel activity and abundance. The ROMK channel is an important pathway for potassium secretion across kidney tubule epithelia.

Drugs that interfere at any point along this system can impair renal potassium secretion and increase the risk of

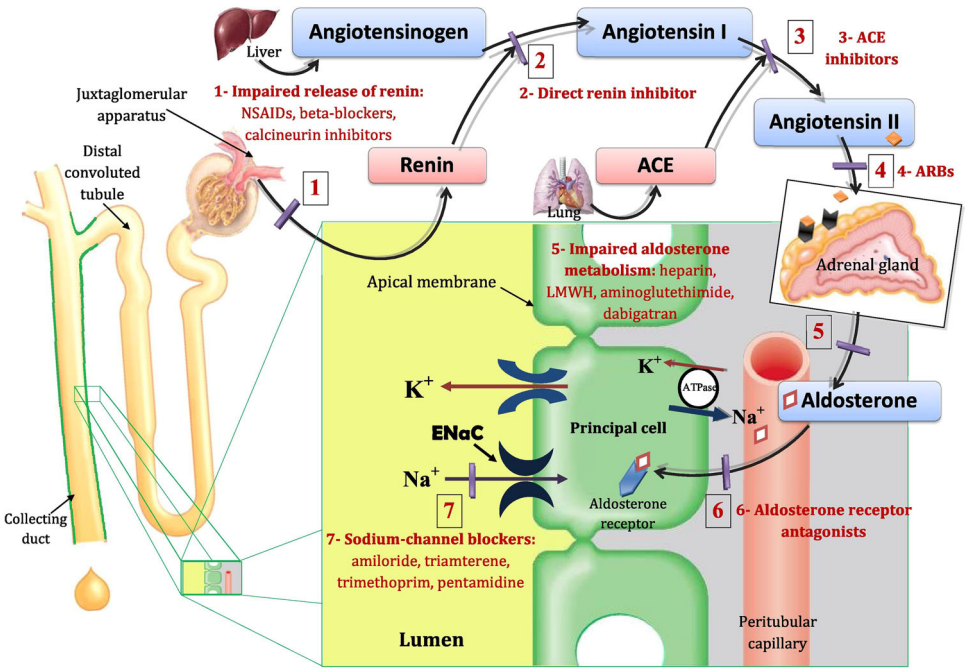

Fig. 1 Drugs that interfere with the renin-angiotensin-aldosterone system, leading to hyperkalemia. *ACE* angiotensin-converting enzyme, *ARBs* angiotensin II receptor blockers, *ATP* adenosine triphosphatase, *ENaC* epithelial sodium channels, *LMWH* low-molecular-weight heparin, *NSAIDs* nonsteroidal anti-inflammatory drugs

hyperkalemia (Fig. 1). They may interfere with aldosterone secretion or action. Hyperkalemia in patients undergoing RAAS blockade is associated with an increased risk of adverse renal and cardiovascular outcomes, especially in patients with CKD [37]. Unfortunately, patients who might benefit from the use of RAAS-blocking agents are those at enhanced risk for development of hyperkalemia.

2.2.1 *Drugs that Affect Aldosterone Secretion*

2.2.1.1 Angiotensin-Converting Enzyme Inhibitors Angiotensin-converting enzyme (ACE) inhibitors impair urinary potassium excretion by interfering with one or more of these three disturbances: aldosterone secretion deficiency in the adrenal gland, decreased delivery of sodium to the distal nephron, and abnormal functioning of the cortical collecting tubule [38]. The incidence of hyperkalemia seems to be relatively low in patients with normal renal function, and serum potassium rarely increases by more than 0.5 mmol/L [4]. However, hyperkalemia becomes increasingly common in those with diminished renal function [39]. The stated incidence of hyperkalemia among patients receiving these drugs varies across studies.

In clinical trials, the risk of hyperkalemia with ACE inhibitor monotherapy in patients with uncomplicated hypertension and without predisposing factors for hyperkalemia is low (≤2%) [40]. The absolute increases in serum potassium levels are small (0.1 mmol/L) and are unlikely to be of clinical significance. Goldberg et al. [41] showed, in a pooled analysis of 16 randomized, double-blind, clinical trials in 2,085 patients with hypertension, that the risk of hyperkalemia (serum potassium ≥5.5 mmol/L) with ACE inhibitor monotherapy was 1.3 % in these patients. The risk of hyperkalemia with ACE inhibitor monotherapy in patients with heart failure or CKD is also increased. The incidence of serum potassium >5.5 mmol/L in patients with severe congestive heart failure was more frequent with the ACE inhibitor enalapril (5–20 mg twice daily; 7.1 %) than with placebo (4.0 %) [39]. However, in these clinical trials, the absolute changes in serum potassium are generally small and unlikely to be clinically significant [40]. However, the rates of hyperkalemia reported in clinical trials of ACE inhibitors may not represent the risk in clinical practice. ACE inhibitor-induced hyperkalemia was relatively frequent among medical outpatients. In fact, hyperkalemia may occur in up to 10 % of outpatients within a year of commencing treatment with an ACE inhibitor [39].

ACE inhibitor therapy is considered a contributing cause in 10–38 % of hospitalized hyperkalemia cases [42]. Additionally, in a recent retrospective study investigating drug-associated life-threatening hyperkalemia (serum potassium concentration >6.5 mmol/L), 47.1 % of cases were associated with an ACE inhibitor.

Patients with moderate-to-severe chronic renal insufficiency, heart failure, diabetes, and diseases associated with impaired response to the potassium secretary effects of aldosterone, especially elderly subjects, are considered as high-risk groups for the development of hyperkalemia by ACE inhibitors [43]. ACE inhibitor-induced hyperkalemia is also more common with concomitant use with medications

known to interfere with the release of renin or with renal potassium excretion. These drugs include aldosterone antagonists, nonsteroidal anti-inflammatory drugs (NSAIDs), calcineurin inhibitors, and beta-blockers [37, 39].

2.2.1.2 Angiotensin-II Receptor Blockers Angiotensin II receptor blockers (ARBs) can cause hyperkalemia by inducing a state of hypoaldosteronism like ACE inhibitors. The incidence of hyperkalemia (potassium levels ≥5.5 mmol/L) seems to not differ between these two classes (1.3 % with ACE inhibitors vs. 1.5 % with losartan) [4]. Although hyperkalemia associated with ARBs is rare in patients without risk factors, it is estimated to be 2–31 % in high-risk patients [44].

Desai et al. [45] reported in the analysis of the CHARM (Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity) program that candesartan significantly increased the rate of aggregate hyperkalemia from 1.8 to 5.2 % and serious hyperkalemia (associated with death or hospitalization) from 1.1 to 1.8 % when compared with placebo. In a randomized, double-blind, multifactorial study in 818 patients with hypertension, monotherapy with telmisartan was associated with small increases in serum potassium of up to 0.131 mmol/L from baseline [44]. The HEAAL (Heart Failure End Point Evaluation of Angiotensin II Antagonist Losartan) study showed that, after 12 months of treatment with losartan (150 mg), serum potassium increased by a mean of 0.02 mmol/L. Serum potassium concentrations were 6.0 mmol/L or greater in 1 % of patients in the 150 mg losartan group [46]. In the post hoc analysis of the RENAAL (Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan) study, including patients with type 2 diabetes and nephropathy, the mean increase of serum potassium levels in the losartan group never exceeded 0.3 mmol/L. Only a small number of patients, 1.1% in the losartan group and 0.5% in the placebo group, had to discontinue therapy because of hyperkalemia. Hyperkalemia associated with losartan is considered clinically manageable in this patient population [47]. However, Miao et al. [48] demonstrated, in a post hoc analysis of the same study, that the occurrence of high serum potassium levels with losartan therapy may increase the risk of adverse renal outcomes and counteract the beneficial renoprotective effects of losartan. They showed for the first time that increased serum potassium concentrations ≥5.0 mmol/L after losartan therapy are associated with a clearly increased risk of doubling of serum creatinine or end-stage renal disease, independent of renal function and other important predictors of renal outcomes. The pathophysiological mechanism whereby increased serum potassium levels affect renal outcomes is not established.

Patients with pre-existing renal insufficiency, diabetes mellitus, or who use other drugs that also impair potassium excretion, such as ACE inhibitors, appear to be more likely to develop hyperkalemia when they are treated with ARBs. As with ACE inhibitors, patients with conditions predisposing to hyperkalemia, and receiving ARBs should be carefully monitored.

2.2.1.3 Direct Renin Inhibitors Aliskiren, the first direct renin inhibitor, inhibits the renin-angiotensin axis at the most proximal step. It has been shown to be efficacious for the management of hypertension, congestive heart failure, and proteinuria [49].

In a recent clinical trial, the proportion of patients with hyperkalemia (serum potassium level ≥6 mmol/L) was significantly higher in the aliskiren group than in the placebo group (11.2 vs. 7.2 %). In addition, hyperkalemia was the most common adverse event leading to the discontinuation of this study drug [50]. The frequency of a maximum serum potassium level above 5.0 mmol/L during this study was 15 % higher among patients with a baseline estimated glomerular filtration rate below 45 ml per minute per 1.73 m^2 than among those with a higher estimated glomerular filtration rate. However, in a pooled analysis of seven randomized, double-blind studies including seven patients with hypertension treated with aliskiren, the incidence of serum potassium 5.5 mmol/L with aliskiren 150 mg/d (0.7 %) and 300 mg/d (1.0 %) was similar to that with placebo (0.6 %) [51].

White et al. [52] showed, in a pooled analysis of clinical experience in more than 12,000 patients with hypertension, that the incidence of potassium levels >5.5 mmol /L with aliskiren monotherapy was similar to that with ARB monotherapy (3.6 vs. 3.3 %, respectively). When combined with an ACE inhibitor or angiotensin receptor blocker, the risk of hyperkalemia with aliskiren was significantly increased as compared with aliskiren monotherapy [49].

2.2.1.4 Nonsteroidal Anti-Inflammatory Drugs NSAIDs have been reported to cause hyperkalemia in patients with or without renal insufficiency [53]. The mechanism of NSAID action is the suppression of prostaglandin-mediated renin release, leading to a state of hyporeninemic hypoaldosteronism [54]. Therefore, the inhibition of prostaglandin I_2 production by NSAIDs may result in hyperkalemia. The decrease in potassium secretion begins to occur with the first dose of NSAID [55].

In addition to inhibiting renin, NSAIDs reduce renal blood flow and the glomerular filtration rate, particularly in the setting of extracellular fluid volume depletion or cardiac failure [56]. The decrease in glomerular filtration rate may further impair potassium excretion.

In patients with normal kidney function, the mean increase in plasma potassium is typically around 0.2 mmol/L. However, in patients with CKD, elevations in plasma potassium can exceed 1 mmol/L [57]. Although the degree of hyperkalemia is often mild, it can be sufficiently severe to cause cardiac arrest and death.

NSAID-induced hyperkalemia is also more likely to occur in patients who have underlying diseases such as cardiac failure or diabetes or who take potassium supplements, potassium-sparing diuretics, or ACE inhibitors [53].

Indomethacin has been reported to cause hyperkalemia in up to 46 % of hospitalized patients in one small uncontrolled observational study [58].

Lafrance and Miller [59] compared the differential risk of hyperkalemia associated with various NSAIDs in large population-based cohorts of NSAID users. They reported that the risk of hyperkalemia (defined as first serum potassium value ≥6.0 mmol/L) did not differ in patients using a single NSAID or two or more NSAIDs as compared with patients no longer using an NSAID. The risk of hyperkalemia varied among individual NSAIDs, ranging from high risks for rofecoxib and indomethacin to low risks for salicylates and the other NSAID groups. Furthermore, the strongest risk factors for NSAID-induced hyperkalemia were a prior episode of hyperkalemia, CKD, diabetes, acute kidney injury, and use of potassium-sparing diuretics. However, the authors of this study used a threshold of 6.0 mmol/L, which may not capture small changes in serum potassium levels associated with NSAIDs. Additionally, they reported that they could not distinguish between genuine and spurious cases of hyperkalemia due to hemolysis in this study.

A retrospective cohort study performed by Aljadhey et al. [60] suggested that selective cyclo-oxygenase (COX)-2 inhibitors may pose a greater risk of hyperkalemia than nonselective NSAIDs. Over the study period, selective COX-2 inhibitor recipients experienced a mean estimated increase in serum potassium concentration of 0.15 mmol/L versus patients prescribed nonselective NSAIDs. The authors postulated that, in contrast to COX-1, COX-2 mediates prostacyclin synthesis, which increases potassium secretion at the distal tubule. Therefore, selective inhibition of COX-2 at the distal tubule could explain the greater risk of hyperkalemia associated with selective COX-2 inhibitors compared with non-selective NSAIDs.

2.2.1.5 Heparin and Derivatives Unfractionated heparin (UH) is an inhibitor of aldosterone production [56]. The aldosterone-inhibitory effect is dose dependent and occurs rapidly following the initiation of therapy [61]. The maximum antagonism of aldosterone effects by heparin occurs after 4–6 days of therapy and may occur at any dosage in clinical use. The aldosterone suppression induced by heparin may be due to various mechanisms. The most important, but probably not the only, mechanism appears to involve reduction in both the number and affinity of the angiotensin II receptors in the zona glomerulosa [62]. Prolonged use of heparin causes microscopic changes and ultrastructural abnormalities of the adrenal zona glomerulosa in experimental studies [62]. Excess anticoagulation with heparin may also, in rare circumstances, precipitate adrenal hemorrhage and induce adrenal insufficiency.

Heparin-induced hyperkalemia (HIH) might occur in approximately 7–8 % of heparin-treated patients [62]. Elevations in serum potassium have ranged from 0.2 to 1.7 mmol/L, with an onset 1–3 days after heparin exposure, and generally resolve within 24 h of heparin discontinuation [27]. HIH can develop irrespective of the dose used and may be seen after either intravenous or subcutaneous administration. Although patients who receive heparin have reduced aldosterone levels, most patients are able to compensate by an increase in renin synthesis to maintain normal potassium values and, therefore, remain asymptomatic [63]. However, patients with diabetes mellitus or renal insufficiency or receiving prolonged heparin therapy or drugs that interfere with potassium excretion are especially predisposed to HIH [64, 65].

Hyperkalemia can also occur in association with low-molecular-weight heparin (LMWH), even at prophylactic doses. In a prospective study, Koren-Michowitz et al. [66] found an early potassium increase, on the third day, in patients treated with therapeutic doses of the LMWH enoxaparin; 9 % of these patients developed potassium levels greater than 5.0 mmol/L. Like UH, mechanisms of LMWH-induced hyperkalemia involve inhibition of aldosterone by reduction in both the number and affinity of angiotensin II receptors in the zona glomerulosa, but an effect on aldosterone synthesis has also been suggested [67]. However, a decrease in aldosterone levels was not demonstrated in all studies [68]. Moreover, a trend towards elevation of renin activity and aldosterone levels were also observed [66].

2.2.1.6 Calcineurin Inhibitors Mild and uncomplicated hyperkalemia is commonly observed in patients treated with calcineurin inhibitors, especially transplant recipients. It has been reported to develop in 44–73 % of transplant recipients who receive immunosuppressive therapy with ciclosporin and tacrolimus [69]. The increased incidence may also be due in part to the development of impaired kidney function in individuals chronically treated with these medications. However, hyperkalemia may occur despite adequate kidney function [70]. Calcineurin inhibitor-induced hyperkalemia may be mediated via a variety of mechanisms. The induction of hypoaldosteronism, the inhibition of potassium secretion at the collecting duct by

inhibiting basolateral Na^+/K^+-ATPase, and leakage of cellular potassium into the extracellular fluid are possible mechanisms [71, 72]. An aldosterone resistance secondary to decreased transcription of human mineralocorticoid receptors on peripheral blood leukocytes is also reported [69]. The use of ACE inhibitors and ARBs to slow the progression of chronic allograft nephropathy can be expected to increase the risk of hyperkalemia with calcineurin inhibitors [38].

2.2.2 *Drugs that Cause Tubular Resistance to the Action of Aldosterone*

A number of drugs can induce hyperkalemia by causing tubular resistance to the action of aldosterone. Aldosterone antagonists block aldosterone binding to mineralocorticoid receptors. Other drugs such as potassium-sparing diuretics (amiloride, triamterene), trimethoprim, and pentamidine may inhibit the activity of the epithelial sodium channel, leading to hyperkalemia.

2.2.2.1 Aldosterone Antagonists Aldosterone antagonists represented by spironolactone and eplerenone block mineralocorticoid receptors present in multiple organs (kidney, colon, and sweat glands). The blockade of renal aldosterone receptors can lead to the development of hyperkalemia. In addition, the mechanism of hyperkalemia might not be limited to decreased renal excretion of K, but probably also involves extrarenal compensatory mechanisms that are partially mediated by aldosterone. In fact, a decreased translocation of extracellular K to intracellular environments, and a decreased gastrointestinal secretion of potassium resulting from blockade of colonic mineralocorticoid receptors, may lead to hyperkalemia [36].

Hyperkalemia usually occurs within the first 10 days. Spironolactone and eplerenone raise plasma potassium an average of 0.2–0.3 mmol/L at a therapeutic dose [73]. The increase in serum potassium seems to be dose related [74]. Hyperkalemia is more likely to occur in the setting of CKD or hypoaldosteronism and depletion of effective plasma volume, such as heart failure and cirrhosis, or when potassium intake is high [56]. Patients with CKD developed a slight but consistent increase in serum levels of potassium during the first 3 months of treatment with aldosterone antagonists [37]. However, spironolactone may also induce life-threatening hyperkalemia, even in the presence of a normal glomerular filtration rate [56]. Significant hyperkalemia after spironolactone administration has also been observed in hemodialysis patients, suggesting that aldosterone can affect the cellular handling of potassium or its gastrointestinal excretion [47]. Combination therapy with other drugs that cause hyperkalemia is another important factor in the predisposition to development of hyperkalemia with aldosterone antagonists. In fact, these drugs are frequently administered in combination with suppressors of RAAS used for the treatment of arterial hypertension or in heart failure such as ACE inhibitors, ARBs, direct renin inhibitors, and beta blockers. All these drugs can facilitate the development of hyperkalemia due to decreased aldosterone secretion.

RALES (Randomized Aldactone Evaluation Study) showed that the addition of spironolactone to standard treatment for patients with congestive cardiac failure is associated with significant reduction in morbidity and mortality [75]. Serious hyperkalemia occurred in only 2 % of patients in the study, where the average serum creatinine concentration was 106 μmol/L and the dose of spironolactone did not exceed 25 mg daily. In EPHESUS (Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study, eplerenone also showed a significantly reduced all-cause mortality and cardiovascular mortality or hospitalization when used in addition to standard therapy in patients with left ventricular systolic dysfunction, left ventricular ejection fraction 40 %, and heart failure after acute myocardial infarction. Serious hyperkalemia (serum potassium >6 mmol/L) occurred more frequently with eplerenone (5.5 %) than with placebo (3.9 %), particularly in those patients with a baseline creatinine clearance of <50 mL/min. The post hoc analyses of EPHESUS demonstrated that eplerenone, when administered at a dose of 25–50 mg/d, is associated with a 4.4 % absolute increase in the incidence of hyperkalemia (5.5 mmol/L) and a 1.6 % absolute increase in the incidence of more marked hyperkalemia (6.0 mmol/L) [76].

After the publication of RALES, the use of aldosterone antagonists was recommended whenever possible in addition to renin-angiotensin system blockade and beta blockers.

By contrast, Juurlink et al. [77] showed that, in a population-based time series analysis, as prescriptions increased from 34 per 1,000 patients in 1994 to 149 per 1,000 in 2001 after the publication of RALES in 1999, hyperkalemia-related hospitalizations increased from 2.4 to 11 per 1,000 patients, and hyperkalemia-associated deaths increased from 0.3 to 2.0 per 1,000 patients.

In a retrospective case series of 64 patients hospitalized with heart failure treated with spironolactone, Dinsdale et al. [78] reported a rate of 11 % for severe hyperkalemia (>6.0 mmol/L), and a rate of 36 % for hyperkalemia (>5.5 mmol/L). Wei et al. [79] reported a 2.9 % incidence of severe hyperkalemia (>6 mmol/L) in a large nonrandomized cohort of heart failure patients. In this study, patients with higher baseline creatinine or potassium levels were at a higher risk of severe hyperkalemia. In a series of 788 hospitalized patients treated with spironolactone, 9 % developed clinically significant hyperkalemia [80]. A study

of outpatient heart failure showed that the use of spironolactone was associated with a high incidence of hyperkalemia (36 % with potassium >5 mmol/L, 10 % with potassium >6 mmol/L) [81].

The relative lower incidence and risk of hyperkalemia associated with aldosterone antagonists in EPHESUS and RALES compared with that observed in clinical practice can be attributed to many factors. In fact, the patients enrolled in these studies had rather mild kidney dysfunction (serum creatinine <221 μmol/L or glomerular filtration rate >30 ml/min/1.73 m^2) and baseline levels of potassium within the normal range (<5.0 mmol/L). Furthermore, in clinical practice, patients are often older than in randomized trials, and were given higher doses of spironolactone and were most likely taking potassium supplements or other drugs that alter potassium excretion.

2.2.2.2 Potassium-Sparing Diuretics Amiloride and triamterene block luminal sodium channels in the collecting tubule and collecting ducts. Blockade of sodium reabsorption through this channel abolishes the negative potential of the lumen and therefore removes a major driving force for the secretion of potassium. These drugs generally cause hyperkalemia within the first 10 days of use. They tend to be relatively ineffective when used as monotherapy for hypertension but can be useful in combination with hydrochlorothiazide [82].

In a small study including 12 mildly hypertensive patients, the average plasma potassium was significantly higher ($P = 0.011$) with amiloride (4.6 mmol/L) than before treatment (4.2 mmol/L). However, no individual value was higher than the upper limit of the normal range, and the highest value recorded was 5.1 mmol/L [83]. The risk of hyperkalemia is increased in the presence of renal impairment. This risk can also be enhanced by concomitant therapy with an ACE inhibitor or ARB. In five patients with diabetes mellitus over 50 years of age who were receiving an ACE inhibitor, the serum potassium rose markedly 8–18 days after the addition of amiloride [84]. Potassium levels were between 9.4 and 11 mmol/L in four of the patients; two did not respond to resuscitation measures.

Quan and Kahana [85] found potassium levels >5.5 mmol/L in 6 of 16 hospitalized patients with congestive heart failure and in 4 of 30 outpatients with varied causes of edema treated with triamterene and hydrochlorothiazide. Severe hyperkalemia (potassium levels 6.0–7.0 mmol/L) has also been reported with triamterene. In another study, Cohen [86] reported a rise in average serum potassium in ten elderly men with congestive heart failure who were treated with a combination of 100 mg of triamterene and 0.5 g of chlorothiazide. In five patients, the serum potassium rose above 6 mmol/L. In addition, he reported the death of two patients in whom hyperkalemia induced by a mixture of triamterene and hydrochlorothiazide was thought to be a contributing factor. In a small study, treatment with the combination of triamterene (50 mg) and hydrochlorothiazide (25 mg) resulted in hyperkalemia in 26 % of the patients [87].

2.2.2.3 Trimethoprim Trimethoprim is a commonly used antibiotic that is employed extensively in combination with sulfamethoxazole (as co-trimoxazole) to treat a number of infections. It reduces renal potassium excretion through the competitive inhibition of epithelial sodium channels in the distal nephron, in a manner similar to amiloride causing hyperkalemia through this mechanism [88]. On the basolateral membrane of the cortical collecting duct, trimethoprim inhibits Na^+/K^+-ATPase, which further reduces the ability of the kidney to excrete potassium [89]. The development of hyperkalemia in association with trimethoprim therapy was first described in patients who were receiving high doses (trimethoprim 20 mg/kg/d) [90]. Hyperkalemia complicating standard dosage (≤320 mg/kg/day) co-trimoxazole treatment has also been reported.

An increase in serum potassium level, which ranges from 0.36 to 1.21 mmol/L or greater, occurs in most (76–100 %) patients who receive trimethoprim [91, 92]. It occurs after approximately 3–10 days of therapy with trimethoprim. Treatment with ACE inhibitors, ARBs, NSAIDs, or spironolactone may exacerbate the hyperkalemic effect of trimethoprim. A recent population-based case-control study involving 439,677 patients taking ACE inhibitors or ARBs found a sevenfold increased risk of hospital admission for hyperkalemia among those taking trimethoprim-sulfamethoxazole compared with those taking other antibiotics used for the urinary tract [93].

2.2.2.4 Pentamidine Pentamidine, an antimicrobial medication, inhibits distal nephron reabsorption of Na^+ by blocking apical Na^+ channels in a manner similar to potassium-sparing diuretics (amiloride, triamterene) [94]. In experimental studies, an antikaliuretic effect of pentamidine was noted at doses ranging from 3 to 10 mg/kg [95]. The antikaliuresis was also accompanied by a marked decrease of urinary sodium and chloride excretion. Pentamidine administration appears to be causally related to life-threatening hyperkalemia in the presence of a mild reduction in creatinine clearance in some patients and to severe acute renal failure in others [96]. In a 5-year retrospective review of adverse drug reactions in HIV-infected patients who were receiving intravenous pentamidine therapy for *Pneumocystis carinii* pneumonia, hyperkalemia (mean potassium level 5.9 mmol/L; range 5.5–6.9) occurred in 19 % of these patients [97]. In another study, Briceland and Bailie [98] reported that nine of 37 (24 %)

AIDS patients treated with pentamidine became hyperkalemic. Total dose and days to hyperkalemia onset were 2,510 ± 1,460 mg and 9.2 ± 4.9 days (range 3–16), respectively. In this study, no correlation between hyperkalemia or nephrotoxicity and initial renal function was found.

2.3 Potassium-Containing Agents

Excessive potassium ingestion rarely induces hyperkalemia in the absence of an underlying defect in potassium homeostasis. A single oral dose of potassium chloride <0.5 meq/kg produces minimal or small increase in a healthy man. Doses of approximately 1 meq/kg increase serum potassium by as much as 1 meq/L [99].

The Boston Collaborative Drug Surveillance Program demonstrated a 3.6 % incidence of hyperkalemia among 4,921 patients taking physician-prescribed potassium supplements. The risk of hyperkalemia was higher among the elderly and those with azotemia. In another study, 4 % of patients receiving potassium chloride supplements developed hyperkalemia [100].

Salt substitutes and salt alternatives, an overlooked dietary potassium source, may cause hyperkalemia. Severe hyperkalemia from these substances is extremely rare if kidney function is normal because of potassium adaptation [101]. However, patients with renal failure or with diabetes mellitus and hyporeninemic hypoaldosteronism may fail to excrete the excess potassium load, resulting in life-threatening hyperkalemia [102]. Case reports of severe hyperkalemia with salt substitutes as a result of its concomitant use with ACE inhibitors, potassium-sparing diuretics, or angiotensin receptor blockers have also been reported [103].

Low-sodium salt such as solo, a healthy alternative to sea salt and sanctioned by medical professionals to contain "near perfect" proportions of potassium, may lead to hyperkalemia in vulnerable patients [104].

Citrate may be supplied as either a potassium salt, a sodium salt, or a sodium-potassium salt. Potassium citrate may be used for alkalinization of urine. Prolonged or excessive ingestion of potassium citrate may lead to severe hyperkalemia [105].

Drugs such as penicillin G may be another source of potassium. Penicillin G is usually administered as the potassium salt and sometimes as the sodium salt of 6-phenylacetamidopenicillanic acid. It contains 1.7 mmol of potassium per million units. It can significantly alter potassium balance when given in very high doses. Severe hyperkalemia with cardiac arrest caused by penicillin is reported [106]. Rapid intravenous infusion or oral administration of large amounts of semisynthetic penicillin derivatives may be potentially dangerous in patients with diabetes and renal insufficiency [106].

Stored blood products may contain a large load of potassium. In a study of 803 adult patients receiving ≥5 U of red blood cells (RBCs) during orthotopic liver transplant, Chen et al. [107] demonstrated that transfusion of RBCs stored for longer periods of time was associated with significantly higher intraoperative mean K^+ concentrations and a higher incidence of hyperkalemia. The blood storage age correlated with the highest K^+ concentrations during the post-reperfusion periods. The low temperature used during RBC preservation shuts down the Na^+/K^+-ATPase pump, slowly leaking potassium out of RBCs. The concentration of extracellular K^+ in the storage medium typically increases at a rate of about 1 mmol/day [108].

2.4 Miscellaneous Agents

In addition to the drugs listed above, miscellaneous agents may also induce hyperkalemia (Table 2) [109–121].

3 Prevention and Management

It is preferable to prevent than to treat drug-induced hyperkalemia. Prevention of drug-induced hyperkalemia should be the physician's first priority. An awareness of drugs leading to hyperkalemia and the need for potassium monitoring, especially in patients with compromised potassium regulation is essential to reduce the risk of hyperkalemia. A combination of medications known to have a potentially hyperkalemic action further increases this risk.

Aldosterone antagonist use might be restricted to patients with high levels of mineralocorticoid activity. In addition, reviewing the patient's diet and concomitant medications might prove useful in reducing the risk of developing subsequent hyperkalemia [37]. In fact, dietary management of potassium intake is an important approach to avoid the development of hyperkalemia. The patient's concurrent medications known to have a potential hyperkalemic action should be avoided if not necessary.

The use of submaximal doses of aldosterone antagonists (<25 mg per day for spironolactone; <50 mg per day for eplerenone) has proven to be a successful strategy in preventing the occurrence of hyperkalemia [37].

Individuals who received potassium monitoring were significantly less likely to experience a hyperkalemia-associated adverse outcome than individuals who did not receive monitoring [122]. The plasma potassium concentration should be measured at the outset to establish a baseline and again within 5–10 days [90]. However,

Table 2 Miscellaneous drugs inducing hyperkalemia and their suggested mechanism

Drug	Clinical setting	K+ mmol/L	Suggested mechanism
Amphotericin [109]	Patients with systemic candida infection	6.7–16	K+ efflux from fungal abscesses
Dabigatran [110]	Renal transplant recipient with mitral valve replacement	5.6	Hyporeninemic–hypoaldosteronism
Hydroxycarbamide [111]	Patient with iliofemoral vein thrombosis	6.7	Unknown
Magnesium sulfate [112]	Patient with severe preeclampsia and acute renal dysfunction	5.9	Unknown
Nafamostat mesilate [113]	Patient with acute pancreatitis	6.3	Inhibition of the ENaC
Nafarelin [114]	Patient with uterine leiomyomas	>10	Unknown
Nicorandil [115]	Patient with hypertension and end-stage renal disease	7	Excessive K_{ATP} channel activation
Octreotide [116]	Patient on hemodialysis with sulphonylurea-induced hypoglycemia	7.3	Suppression of insulin release with impair of cellular K+ uptake
Omeprazole [117, 118]	Patient with gastric ulcer	6.6	Decrease of K+ loss from GI tract. Impaired production of aldosterone
Propofol [119]	Patient undergoing dilation and curettage for intrauterine fetal death	9.1	Transcelluar K + shift
Thalidomide [120]	Patients with myeloma and moderate to severe renal failure	7.5–9.1	Unknown
Zoledronic acid [121]	Patient with Paget's disease. Normal renal function	6.3	Unknown

ENaC epithelial sodium channels, *GI* gastrointestinal, *K+* potassium

hyperkalemia may persist throughout the whole treatment period.

The occurrence of hyperkalemia after the use of ACE inhibitors/ARBs is of particular concern. Indeed, patients at highest risk of this side effect are often those who had the greatest cardiovascular benefit. When they are used in patients with severe reductions in the glomerular filtration rate, close monitoring is required to minimize the risk of hyperkalemia [38]. Among patients with CKD, co-prescribing an ACE inhibitor and an ARB or an ACE inhibitor or ARB with a potassium-sparing diuretic should be avoided. However, if a patient is currently receiving a loop or a thiazide diuretic that increases potassium excretion, it should be continued. Prior to the administration of the ACE inhibitor/ARB, the physician should review the patient's medication profile and, whenever possible, withdraw drugs that can impair potassium excretion. In fact, in patients receiving a combination of an ACE inhibitor, an ARB, a beta-blocker, and an aldosterone antagonist, discontinuation of one drug, whenever possible, may also be useful for lowering the serum potassium concentration. It is also prudent to start with low doses and titrate cautiously to higher doses. Serum potassium should be monitored within the first week of therapy and again after any dosage increase [42]. For increased serum potassium concentrations of up to 5.5 mmol/L, the dose can be lowered, and if the potassium concentration decreases, the treatment with these drugs can be continued [38].

Given the number of patients who take therapy with NSAIDs on a prescription or over-the-counter basis, the absolute number of patients at high risk is relatively large. Patients at high risk for hyperkalemia include the elderly, dehydrated individuals, those with pre-existing renal disease, and patients taking potassium-sparing diuretics, potassium supplements, ACE inhibitors, and beta blockers. Therefore, the dose should be reduced in these patients. Some authors also recommended a measure of potassium within 1–3 weeks, repeated every 3–6 months [57, 123]. However, prescription of NSAIDs should not exceed a few days. Patients should be advised to avoid potassium supplements, and to discontinue the NSAID and contact their physician if they develop diarrhea or vomiting, as these problems increase the risk of hyperkalemia and acute renal insufficiency when they occur in association with NSAID therapy [90]. Alternative therapeutics such as non-NSAID analgesics or topical balms may also be considered.

Because of the widespread and increasing use of UH and LMWH, clinicians must be cautious regarding hyperkalemia. It is recommended that monitoring for hyperkalemia be performed at 3- to 4-day intervals in patients receiving prolonged heparin, including deep venous thrombosis prophylaxis [57].

Currently, antimicrobial therapies with co-trimoxazole (trimethoprim-sulfamethoxazole) or penicillin are widely prescribed. In patients treated with high-dosage trimethoprim or with renal insufficiency, serum potassium level should be monitored to identify the development of hyperkalemia. In patients receiving standard dosage and in the presence of one or more risk factors, such as older age, hypoaldosteronism, or treatment with hyperkalemia-inducing medications, serum potassium should be measured after approximately 3 days of treatment with trimethoprim [91]. Serum potassium concentrations should be also closely monitored if high doses of penicillin are

administered, particularly in patients with diabetes, renal insufficiency, or congestive heart failure [106].

Most guidelines and experts advise that management of hyperkalemia should be guided by the serum potassium level [1, 2, 124, 125]. Therapeutic strategies should be aimed at restoring normal serum and total-body stores of potassium and preventing serious complications.

For mild hyperkalemia (5–6 mmol/L), Drug-induced hyperkalemia should be minimized or withdrawn if not necessary and dietary potassium restricted when possible. Loop or thiazide diuretics and sodium polystyrene sulfonate (SPS) should be used. Diuretics enhance renal potassium excretion by increasing the distal delivery of sodium and urine flow rate. Therefore, these drugs are efficacious in patients with adequate renal function. However, many patients with hyperkalemia have underlying kidney failure that limits their efficacy.

SPS, a cation-exchange resin, can be administered orally or rectally by enema. It is relatively slow acting, and a significant reduction in serum potassium may not be observed for 4–6 h [126]. Whole-body fluid overload and colonic perforation have been reported with SPS use.

In moderate hyperkalemia (6–7 mmol/L), an intracellular shift of K^+ should be achieved using an insulin-glucose drip, sodium bicarbonate, and a beta2 agonist. The hypokalemic effect of insulin is dose dependent. It can be seen within 20 min, peaking between 30 and 60 min, and is unaffected by kidney failure. Beta2 agonists administered intravenously, via nebulizer or via metered dose inhaler, lower serum potassium by 0.5–1.5 mmol/L. The potassium-lowering effect of these drugs in patients with impaired renal function is unpredictable. The doses of inhaled beta2 agonists used for hyperkalemia are higher than those typically used for bronchospasm. Salbutamol is the most commonly used selective beta2 agonist. Salbutamol can be used alone or to augment the effect of insulin. It seems that there is no evidence of benefit in the use of beta2 agonists where insulin (and dextrose) can be safely administered [127].

The hypokalemic effect of sodium bicarbonate is small, delayed in onset, and unpredictable [2]. Hence, this agent should not be relied on as initial or monotherapy to treat hyperkalemia. Its use may be beneficial for patients who also have severe metabolic acidosis by raising the extracellular pH, in addition to causing a rapid intracellular potassium shift. Sodium bicarbonate can also lead to sodium and volume overload in patients with CKD, which may worsen hypertension and contribute to the development of acute congestive heart failure.

In severe hyperkalemia (>7mmol/L with toxic electrocardiogram [ECG] changes) calcium gluconate (or chloride) can be used as an infusion to achieve membrane stabilization. Calcium antagonizes the effects of hyperkalemia on cardiac conduction, and is effective even in normocalcemic patients.

Calcium can be administered as either calcium gluconate or calcium chloride. Because calcium chloride is more likely to cause tissue necrosis with extravasation, calcium gluconate is preferred. However, calcium chloride provides approximately three times more calcium than equal volumes of the gluconate salt. Therefore, the dose needs to be attenuated accordingly to avoid potential calcium toxicity. Caution should also be exercised when calcium is administered in patients receiving digoxin because it potentiates myocardial toxicity to digoxin. However, in recent studies among digoxin-intoxicated humans, intravenous calcium does not seem to cause malignant dysrhythmias or increase mortality [128].

In addition to calcium, all the modalities mentioned above should be employed to lower serum potassium levels. Hemodialysis should be considered the primary method of potassium removal in refractory cases of hyperkalemia and if a patient has renal failure and a diuretic may not be effective [126].

Fludrocortisone, a mineralocorticoid, increases urinary potassium excretion. It has been used to treat calcineurin inhibitor-associated hyperkalemia [129]. It is also proposed to treat hyperkalemia secondary to heparin when the continuing administration of heparin is necessary.

4 Conclusions

In conclusion, a wide range of drugs can cause hyperkalemia via different mechanisms. Drug-induced hyperkalemia may be asymptomatic. However, it may be dramatic and life threatening, posing diagnostic and management problems. Prevention is based on the awareness of this complication. Appropriate management requires knowledge of the mechanism of the development of hyperkalemia, as well as a therapeutic strategy based not only on the serum potassium level, but also on the severity of clinical presentation, electrocardiographic features, acid base, and metabolic abnormalities, as well as organ function disturbances.

Acknowledgments No sources of funding were used to assist in the preparation of this study. Chaker Ben Salem, Atef Badreddine, Neila Fathallah, Raoudha Slim and Houssem Hmouda have no conflicts of interest that are directly relevant to the content of this study.

References

1. Sood MM, Sood AR, Richardson R. Emergency management and commonly encountered outpatient scenarios in patients with hyperkalemia. Mayo Clin Proc. 2007;82(12):1553–61.
2. Evans KJ, Greenberg A. Hyperkalemia: a review. J Intensive Care Med. 2005;20(5):272–90.

3. Perazella MA. Drug-induced hyperkalemia: old culprits and new offenders. Am J Med. 2000;109(4):307–14.
4. Miltiadous G, Mikhailidis DP, Elisaf M. Acid-base and electrolyte abnormalities observed in patients receiving cardiovascular drugs. J Cardiovasc Pharmacol Ther. 2003;8(4):267–76.
5. Passare G, Viitanen M, Torring O, Winblad B, Fastbom J. Sodium and potassium disturbances in the elderly: prevalence and association with drug use. Clin Drug Investig. 2004;24(9):535–44.
6. Noize P, Bagheri H, Durrieu G, Haramburu F, Moore N, Giraud P, et al. Life-threatening drug-associated hyperkalemia: a retrospective study from laboratory signals. Pharmacoepidemiol Drug Saf. 2011;20(7):747–53.
7. Banerjee A, Stoica C, Walia A. Acute hyperkalemia as a complication of intravenous therapy with epsilon-aminocaproic acid. J Clin Anesth. 2011;23(7):565–8.
8. Barone R, Pauwels S, De Camps J, Krenning EP, Kvols LK, Smith MC, et al. Metabolic effects of amino acid solutions infused for renal protection during therapy with radiolabelled somatostatin analogues. Nephrol Dial Transplant. 2004;19(9):2275–81.
9. Giovacchini G, Nicolas G, Freidank H, Mindt TL, Forrer F. Effect of amino acid infusion on potassium serum levels in neuroendocrine tumour patients treated with targeted radiopeptide therapy. Eur J Nucl Med Mol Imaging. 2011;38(9):1675–82.
10. Hertz P, Richardson JA. Arginine-induced hyperkalemia in renal failure patients. Arch Intern Med. 1972;130(5):778–80.
11. Brass EP, Thompson WL. Drug-induced electrolyte abnormalities. Drugs. 1982;24(3):207–28.
12. Carroll HJ, Tice DA. The effects of epsilon amino-caproic acid upon potassium metabolism in the dog. Metabolism. 1966;15(5):449–57.
13. Nzerue CM, Falana B. Refractory hyperkalaemia associated with use of epsilon-aminocaproic acid during coronary bypass in a dialysis patient. Nephrol Dial Transplant. 2002;17(6):1150–1.
14. Lundborg P. The effect of adrenergic blockade on potassium concentrations in different conditions. Acta Med Scand Suppl. 1983;672:121–6.
15. Sica DA. Antihypertensive therapy and its effects on potassium homeostasis. J Clin Hypertens (Greenwich). 2006;8(1):67–73.
16. Bethune DW, McKay R. Paradoxical changes in serum-potassium during cardiopulmonary bypass in association with non-cardioselective beta blockade. Lancet. 1978;2(8085):380.
17. Swenson ER. Severe hyperkalemia as a complication of timolol, a topically applied beta-adrenergic antagonist. Arch Intern Med. 1986;146(6):1220–1.
18. McCauley J, Murray J, Jordan M, Scantlebury V, Vivas C, Shapiro R. Labetalol-induced hyperkalemia in renal transplant recipients. Am J Nephrol. 2002;22(4):347–51.
19. Castellino P, Simonson DC, DeFronzo RA. Adrenergic modulation of potassium metabolism during exercise in normal and diabetic humans. Am J Physiol. 1987;252(1 Pt 1):E68–76.
20. Arthur S, Greenberg A. Hyperkalemia associated with intravenous labetalol therapy for acute hypertension in renal transplant recipients. Clin Nephrol. 1990;33:269–71.
21. Ben Salem C, Hmouda H, Bouraoui K. Drug-induced hypokalaemia. Curr Drug Saf. 2009;4(1):55–61.
22. Rasmussen L, Husted SE, Johnsen SP. Severe intoxication after an intentional overdose of amlodipine. Acta Anaesthesiol Scand. 2003;47(8):1038–40.
23. Imamura T, Matsuura Y, Nagoshi T, Ishikawa T, Date H, Kita T, et al. Hyperkalemia induced by the calcium channel blocker, benidipine. Intern Med. 2003;42(6):503–6.
24. Freed MI, Rastegar A, Bia MJ. Effects of calcium channel blockers on potassium homeostasis. Yale J Biol Med. 1991;64(2):177–86.
25. Martyn JA, Richtsfeld M. Succinylcholine-induced hyperkalemia in acquired pathologic states: etiologic factors and molecular mechanisms. Anesthesiology. 2006;104(1):158–69.
26. Gronert GA. Succinylcholine-induced hyperkalemia and beyond. 1975. Anesthesiology. 2009;111(6):1372–7.
27. Buckley MS, Leblanc JM, Cawley MJ. Electrolyte disturbances associated with commonly prescribed medications in the intensive care unit. Crit Care Med. 2010;38(6 Suppl):S253–64.
28. Fenton F, Smally AJ, Laut J. Hyperkalemia and digoxin toxicity in a patient with kidney failure. Ann Emerg Med. 1996;28(4):440–1.
29. Manini AF, Nelson LS, Hoffman RS. Prognostic utility of serum potassium in chronic digoxin toxicity: a case-control study. Am J Cardiovasc Drugs. 2011;11(3):173–8.
30. Papadakis MA, Wexman MP, Fraser C, Sedlacek SM. Hyperkalemia complicating digoxin toxicity in a patient with renal failure. Am J Kidney Dis. 1985;5(1):64–6.
31. Moreno M, Murphy C, Goldsmith C. Increase in serum potassium resulting from the administration of hypertonic mannitol and other solutions. J Lab Clin Med. 1969;73(2):291–8.
32. Manninen PH, Lam AM, Gelb AW, Brown SC. The effect of high-dose mannitol on serum and urine electrolytes and osmolality in neurosurgical patients. Can J Anaesth. 1987;34(5):442–6.
33. Sharma J, Salhotra R. Mannitol-induced intraoperative hyperkalemia, a little-known clinical entity. J Anaesthesiol Clin Pharmacol. 2012;28(4):546–7.
34. Tobita K, Kohno T. Case of hyperkalemia after the administration of hypertonic mannitol during craniotomy. Masui. 2010;59(5):641–4.
35. Meneton P, Loffing J, Warnock DG. Sodium and potassium handling by the aldosterone-sensitive distal nephron: the pivotal role of the distal and connecting tubule. Am J Physiol Renal Physiol. 2004;287(4):F593–601.
36. Staruschenko A. Regulation of transport in the connecting tubule and cortical collecting duct. Compr Physiol. 2012;2:1541–84.
37. Roscioni SS, de Zeeuw D, Bakker SJ, Lambers Heerspink HJ. Management of hyperkalaemia consequent to mineralocorticoid-receptor antagonist therapy. Nat Rev Nephrol. 2012;8(12):691–9.
38. Palmer BF. Managing hyperkalemia caused by inhibitors of the renin-angiotensin-aldosterone system. N Engl J Med. 2004;351(6):585–92.
39. Reardon LC, Macpherson DS. Hyperkalemia in outpatients using angiotensin-converting enzyme inhibitors. How much should we worry? Arch Intern Med. 1998;158(1):26–32.
40. Weir MR, Rolfe M. Potassium homeostasis and renin-angiotensin-aldosterone system inhibitors. Clin J Am Soc Nephrol. 2010;5(3):531–48.
41. Goldberg AI, Dunlay MC, Sweet CS. Safety and tolerability of losartan potassium, an angiotensin II receptor antagonist, compared with hydrochlorothiazide, atenolol, felodipine ER, and angiotensin-converting enzyme inhibitors for the treatment of systemic hypertension. Am J Cardiol. 1995;75(12):793–5.
42. Raebel MA. Hyperkalemia associated with use of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers. Cardiovasc Ther. 2012;30(3):e156–66.
43. Cheng H, Harris RC. Potential side effects of renin inhibitors—mechanisms based on comparison with other renin-angiotensin blockers. Expert Opin Drug Saf. 2006;5(5):631–41.
44. Park I, Sheen SS, Lim HS, Yoon D, Park MY, Lee SH, et al. Comparison of hyperkalemic risk in hospitalized patients treated with different angiotensin receptor blockers: a retrospective cohort study using a Korean clinical research database. Am J Cardiovasc Drugs. 2012;12(4):255–62.

45. Desai AS, Swedberg K, McMurray JJ, Granger CB, Yusuf S, Young JB, et al. Incidence and predictors of hyperkalemia in patients with heart failure: an analysis of the CHARM Program. J Am Coll Cardiol. 2007;50(20):1959–66.
46. Konstam MA, Neaton JD, Dickstein K, Drexler H, Komajda M, Martinez FA, et al. Effects of high-dose versus low-dose losartan on clinical outcomes in patients with heart failure (HEAAL study): a randomised, double-blind trial. Lancet. 2009;374(9704):1840–8.
47. Appel GB, Radhakrishnan J, Avram MM, DeFronzo RA, Escobar-Jimenez F, Campos MM, et al. Analysis of metabolic parameters as predictors of risk in the RENAAL study. Diabetes Care. 2003;26(5):1402–7.
48. Miao Y, Dobre D, Heerspink HJ, Brenner BM, Cooper ME, Parving HH, et al. Increased serum potassium affects renal outcomes: a post hoc analysis of the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) trial. Diabetologia. 2011;54(1):44–50.
49. Harel Z, Gilbert C, Wald R, Bell C, Perl J, Juurlink D, et al. The effect of combination treatment with aliskiren and blockers of the renin-angiotensin system on hyperkalaemia and acute kidney injury: systematic review and meta-analysis. BMJ. 2012;344:e42.
50. Parving HH, Brenner BM, McMurray JJ, de Zeeuw D, Haffner SM, Solomon SD, et al. Cardiorenal end points in a trial of aliskiren for type 2 diabetes. N Engl J Med. 2012;367(23):2204–13.
51. Weir MR, Bush C, Anderson DR, Zhang J, Keefe D, Satlin A. Antihypertensive efficacy, safety, and tolerability of the oral direct renin inhibitor aliskiren in patients with hypertension: a pooled analysis. J Am Soc Hypertens. 2007;1(4):264–77.
52. White WB, Bresalier R, Kaplan AP, Palmer BF, Riddell RH, Lesogor A, et al. Safety and tolerability of the direct renin inhibitor aliskiren: a pooled analysis of clinical experience in more than 12,000 patients with hypertension. J Clin Hypertens (Greenwich). 2010;12(10):765–75.
53. Harirforoosh S, Jamali F. Renal adverse effects of nonsteroidal anti-inflammatory drugs. Expert Opin Drug Saf. 2009;8(6):669–81.
54. Bennett WM, Henrich WL, Stoff JS. The renal effects of nonsteroidal anti-inflammatory drugs: summary and recommendations. Am J Kidney Dis. 1996;28(1 Suppl 1):S56–62.
55. Brater DC. Effects of nonsteroidal anti-inflammatory drugs on renal function: focus on cyclooxygenase-2-selective inhibition. Am J Med. 1999;107(6A):65S–70S discussion S-1S.
56. Preston RA, Hirsh MM, Oster MD Jr, Oster HM. University of Miami Division of Clinical Pharmacology therapeutic rounds: drug-induced hyperkalemia. Am J Ther. 1998;5(2):125–32.
57. Khanna A, White WB. The management of hyperkalemia in patients with cardiovascular disease. Am J Med. 2009;122(3):215–21.
58. Zimran A, Kramer M, Plaskin M, Hershko C. Incidence of hyperkalaemia induced by indomethacin in a hospital population. Br Med J (Clin Res Ed). 1985;291(6488):107–8.
59. Lafrance JP, Miller DR. Dispensed selective and nonselective nonsteroidal anti-inflammatory drugs and the risk of moderate to severe hyperkalemia: a nested case-control study. Am J Kidney Dis. 2012;60(1):82–9.
60. Aljadhey H, Tu W, Hansen RA, Blalock S, Brater DC, Murray MD. Risk of hyperkalemia associated with selective COX-2 inhibitors. Pharmacoepidemiol Drug Saf. 2010;19(11):1194–8.
61. Siebels M, Andrassy K, Vecsei P, Seelig HP, Back T, Nawroth P, et al. Dose dependent suppression of mineralocorticoid metabolism by different heparin fractions. Thromb Res. 1992;66(5):467–73.
62. Oster JR, Singer I, Fishman LM. Heparin-induced aldosterone suppression and hyperkalemia. Am J Med. 1995;98(6):575–86.
63. Bhaskar B, Fraser JF, Mullaney D. Lest we forget: heparin-induced hyperkalemia. J Cardiothorac Vasc Anesth. 2012;26(1):106–9.
64. Gheno G, Cinetto L, Savarino C, Vellar S, Carraro M, Randon M. Variations of serum potassium level and risk of hyperkalemia in inpatients receiving low-molecular-weight heparin. Eur J Clin Pharmacol. 2003;59(5–6):373–7.
65. Aull L, Chao H, Coy K. Heparin-induced hyperkalemia. DICP. 1990;24(3):244–6.
66. Koren-Michowitz M, Avni B, Michowitz Y, Moravski G, Efrati S, Golik A. Early onset of hyperkalemia in patients treated with low molecular weight heparin: a prospective study. Pharmacoepidemiol Drug Saf. 2004;13(5):299–302.
67. Danguy C, Biston P, Carlier E, Defrance P, Piagnerelli M. Severe hyperkalemia in critically ill patients treated with prophylactic doses of enoxaparin. Intensive Care Med. 2012;38(11):1904–5.
68. Marcelli JM, Lalau JD, Abourachid H, Quiret JC, Quichaud J. Unlike heparin, low-molecular weight heparin does not suppress aldosterone production. Horm Metab Res. 1989;21(7):402.
69. Rangel EB. The metabolic and toxicological considerations for immunosuppressive drugs used during pancreas transplantation. Expert Opin Drug Metab Toxicol. 2012;8(12):1531–48.
70. Caliskan Y, Kalayoglu-Besisik S, Sargin D, Ecder T. Cyclosporine-associated hyperkalemia: report of four allogeneic blood stem-cell transplant cases. Transplantation. 2003;75(7):1069–72.
71. Laine J, Holmberg C. Renal and adrenal mechanisms in cyclosporine-induced hyperkalaemia after renal transplantation. Eur J Clin Invest. 1995;25(9):670–6.
72. Heering P, Grabensee B. Influence of ciclosporin A on renal tubular function after kidney transplantation. Nephron. 1991;59(1):66–70.
73. Funder JW. Eplerenone: hypertension, heart failure and the importance of mineralocorticoid receptor blockade. Future Cardiol. 2006;2(5):535–41.
74. Nappi JM, Sieg A. Aldosterone and aldosterone receptor antagonists in patients with chronic heart failure. Vasc Health Risk Manag. 2011;7:353–63.
75. Pitt B, Zannad F, Remme WJ, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. N Engl J Med. 1999;341(10):709–17.
76. Pitt B, Bakris G, Ruilope LM, DiCarlo L, Mukherjee R, Investigators E. Serum potassium and clinical outcomes in the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS). Circulation. 2008;118(16):1643–50.
77. Juurlink DN, Mamdani MM, Lee DS, Kopp A, Austin PC, Laupacis A, et al. Rates of hyperkalemia after publication of the Randomized Aldactone Evaluation Study. N Engl J Med. 2004;351(6):543–51.
78. Dinsdale C, Wani M, Steward J, O'Mahony MS. Tolerability of spironolactone as adjunctive treatment for heart failure in patients over 75 years of age. Age Ageing. 2005;34(4):395–8.
79. Wei L, Struthers AD, Fahey T, Watson AD, Macdonald TM. Spironolactone use and renal toxicity: population based longitudinal analysis. BMJ. 2010;340:c1768.
80. Greenblatt DJ, Koch-Weser J. Adverse reactions to spironolactone. A report from the boston collaborative drug surveillance program. JAMA. 1973;225(1):40–3.
81. Svensson M, Gustafsson F, Galatius S, Hildebrandt PR, Atar D. How prevalent is hyperkalemia and renal dysfunction during treatment with spironolactone in patients with congestive heart failure? J Card Fail. 2004;10(4):297–303.
82. Epstein M, Calhoun DA. Aldosterone blockers (mineralocorticoid receptor antagonism) and potassium-sparing diuretics. J Clin Hypertens (Greenwich). 2011;13(9):644–8.

83. Paterson JW, Dollery CT, Haslam RM. Amiloride hydrochloride in hypertensive patients. Br Med J. 1968;1(5589):422–3.
84. Chiu TF, Bullard MJ, Chen JC, Liaw SJ, Ng CJ. Rapid life-threatening hyperkalemia after addition of amiloride HCl/hydrochlorothiazide to angiotensin-converting enzyme inhibitor therapy. Ann Emerg Med. 1997;30(5):612–5.
85. Quan KC, Kahana L. Clinical experience with the diuretic effects of triamterene alone and combined with hydrochlorothiazide. Curr Ther Res Clin Exp. 1964;6:27–34.
86. Cohen AB. Hyperkalemic effects of triamterene. Ann Intern Med. 1966;65(3):521–7.
87. Petersen AG. Letter: dyazide and hyperkalemia. Ann Intern Med. 1976;84(5):612–3.
88. Choi MJ, Fernandez PC, Patnaik A, Coupaye-Gerard B, D'Andrea D, Szerlip H, et al. Brief report: trimethoprim-induced hyperkalemia in a patient with AIDS. N Engl J Med. 1993;328(10):703–6.
89. Zietse R, Zoutendijk R, Hoorn EJ. Fluid, electrolyte and acid-base disorders associated with antibiotic therapy. Nat Rev Nephrol. 2009;5(4):193–202.
90. Perazella MA, Mahnensmith RL. Hyperkalemia in the elderly: drugs exacerbate impaired potassium homeostasis. J Gen Intern Med. 1997;12(10):646–56.
91. Perazella MA. Trimethoprim-induced hyperkalaemia: clinical data, mechanism, prevention and management. Drug Saf. 2000;22(3):227–36.
92. Ackerman BH, Patton ML, Guilday RE, Haith LR Jr, Stair-Buchmann M, Reigart CL. Trimethoprim-induced hyperkalemia in burn patients treated with intravenous or oral trimethoprim sulfamethoxazole for methicillin-resistant Staphylococcus aureus and other infections: nature or nurture? J Burn Care Res. 2013;34(1):127–32.
93. Antoniou T, Gomes T, Juurlink DN, Loutfy MR, Glazier RH, Mamdani MM. Trimethoprim-sulfamethoxazole-induced hyperkalemia in patients receiving inhibitors of the renin-angiotensin system: a population-based study. Arch Intern Med. 2010;170(12):1045–9.
94. Kleyman TR, Roberts C, Ling BN. A mechanism for pentamidine-induced hyperkalemia: inhibition of distal nephron sodium transport. Ann Intern Med. 1995;122(2):103–6.
95. Gabriels G, Stockem E, Greven J. Potassium-sparing renal effects of trimethoprim and structural analogues. Nephron. 2000;86(1):70–8.
96. Buff DD, Aboal AA. Pentamidine-associated renal dysfunction and hyperkalemia. Am J Med. 1990;88(5):552.
97. O'Brien JG, Dong BJ, Coleman RL, Gee L, Balano KB. A 5-year retrospective review of adverse drug reactions and their risk factors in human immunodeficiency virus-infected patients who were receiving intravenous pentamidine therapy for Pneumocystis carinii pneumonia. Clin Infect Dis. 1997;24(5):854–9.
98. Briceland LL, Bailie GR. Pentamidine-associated nephrotoxicity and hyperkalemia in patients with AIDS. DICP. 1991;25(11):1171–4.
99. Perez GO, Oster JR, Pelleya R, Caralis PV, Kem DC. Hyperkalemia from single small oral doses of potassium chloride. Nephron. 1984;36(4):270–1.
100. Lawson DH. Adverse reactions to potassium chloride. Q J Med. 1974;43(171):433–40.
101. John SK, Rangan Y, Block CA, Koff MD. Life-threatening hyperkalemia from nutritional supplements: uncommon or undiagnosed? Am J Emerg Med. 2011;29(9):1237e1–2.
102. Doorenbos CJ, Vermeij CG. Danger of salt substitutes that contain potassium in patients with renal failure. BMJ. 2003;326(7379):35–6.
103. Ray K, Dorman S, Watson R. Severe hyperkalaemia due to the concomitant use of salt substitutes and ACE inhibitors in hypertension: a potentially life threatening interaction. J Hum Hypertens. 1999;13(10):717–20.
104. Dent A, Walmsley D, Dhandapani S. Hyperkalaemia is a risk with low sodium salt in vulnerable patients. BMJ. 2011;343:d4514.
105. Lyons KS, McGlinchey P. Hyperkalaemic cardiac arrhythmia due to prolonged ingestion of potassium citrate. Int J Cardiol. 2009;131(3):e134–6.
106. Thiele A, Rehman HU. Hyperkalemia caused by penicillin. Am J Med. 2008;121(8):e1–2.
107. Chen J, Singhapricha T, Memarzadeh M, Ziman A, Yuan S, Hu KQ, et al. Storage age of transfused red blood cells during liver transplantation and its intraoperative and postoperative effects. World J Surg. 2012;36(10):2436–42.
108. Zimrin AB, Hess JR. Current issues relating to the transfusion of stored red blood cells. Vox Sang. 2009;96(2):93–103.
109. Barcia JP. Hyperkalemia associated with rapid infusion of conventional and lipid complex formulations of amphotericin B. Pharmacotherapy. 1998;18(4):874–6.
110. Zaleski M, Dabage N, Paixao R, Muniz J. Dabigatran-induced hyperkalemia in a renal transplant recipient: a clinical observation. J Clin Pharmacol. 2013;53(4):456–8.
111. Marusic S, Gojo-Tomic N, Bacic-Vrca V, Bozikov V. Hyperkalaemia associated with hydroxyurea in a patient with polycythaemia vera. Eur J Clin Pharmacol. 2011;67(7):757–8.
112. Iglesias MH, Giesbrecht EM, von Dadelszen P, Magee LA. Postpartum hyperkalemia associated with magnesium sulfate. Hypertens Pregnancy. 2011;30(4):481–4.
113. Kitagawa H, Chang H, Fujita T. Hyperkalemia due to nafamostat mesylate. N Engl J Med. 1995;332(10):687.
114. Hata T, Hata K, Kawamura T. Severe hyperkalaemia with nafarelin. Lancet. 1996;347(8997):333.
115. Lee HH, Hsu PC, Lin TH, Lai WT, Sheu SH. Nicorandil-induced hyperkalemia in a uremic patient. Case Rep Med. 2012;2012:812178.
116. Adabala M, Jhaveri KD, Gitman M. Severe hyperkalaemia resulting from octreotide use in a haemodialysis patient. Nephrol Dial Transplant. 2010;25(10):3439–42.
117. Tashiro M, Yoshikawa I, Kume K, Narita R, Sugihara Y, Otsuki M. Acute hyperkalemia associated with intravenous omeprazole therapy. Am J Gastroenterol. 2003;98(5):1209–10.
118. Gau JT, Heh V, Acharya U, Yang YX, Kao TC. Uses of proton pump inhibitors and serum potassium levels. Pharmacoepidemiol Drug Saf. 2009;18(9):865–71.
119. Lee JH, Ko YS, Shin HJ, Yi JH, Han SW, Kim HJ. Is There a Relationship between Hyperkalemia and Propofol? Electrolyte Blood Press. 2011;9(1):27–31.
120. Harris E, Behrens J, Samson D, Rahemtulla A, Russell NH, Byrne JL. Use of thalidomide in patients with myeloma and renal failure may be associated with unexplained hyperkalaemia. Br J Haematol. 2003;122(1):160–1.
121. Panteliou E, Young N, Naysmith M. Life-threatening hyperkalemia following zoledronic acid infusion for Paget's disease: a case report. J Med Case Rep. 2011;5:367.
122. Raebel MA, Ross C, Xu S, Roblin DW, Cheetham C, Blanchette CM, et al. Diabetes and drug-associated hyperkalemia: effect of potassium monitoring. J Gen Intern Med. 2010;25(4):326–33.
123. Bush TM, Shlotzhauer TL, Imai K. Nonsteroidal anti-inflammatory drugs. Proposed guidelines for monitoring toxicity. West J Med. 1991;155(1):39–42.
124. Hoskote SS, Joshi SR, Ghosh AK. Disorders of potassium homeostasis: pathophysiology and management. J Assoc Physicians India. 2008;56:685–93.
125. ECC Committee, Subcommittees and Task Forces of the American Heart Association. 2005 American Heart Association

Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation. 2005;112(24 Suppl): IV1-203.
126. Weiner ID, Wingo CS. Hyperkalemia: a potential silent killer. J Am Soc Nephrol. 1998;9(8):1535–43.
127. Chapagain A, Ashman N. Hyperkalaemia in the age of aldosterone antagonism. QJM. 2012;105(11):1049–57.
128. Levine M, Nikkanen H, Pallin DJ. The effects of intravenous calcium in patients with digoxin toxicity. J Emerg Med. 2011;40(1):41–6.
129. Dick TB, Raines AA, Stinson JB, Collingridge DS, Harmston GE. Fludrocortisone is effective in the management of tacrolimus-induced hyperkalemia in liver transplant recipients. Transplant Proc. 2011;43(7):2664–8.