

# Drug-induced hyperkalemia: old culprits and new offenders

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## Abstract

Prescribed medications, over-the-counter drugs, and nutritional supplements are used by many patients. Although most of these products are well tolerated, drug-induced hyperkalemia may develop in patients with underlying renal impairment or other abnormalities in potassium handling. Drug-induced hyperkalemia most often occurs from impaired renal potassium excretion. However, disturbed cellular uptake of a potassium load as well as excessive ingestion or infusion of potassium-containing substances may also occur. Physicians must be aware of medications that can precipitate hyperkalemia, how these drugs induce alterations in potassium homeostasis, and the patient characteristics that increase the risk of hyperkalemia.

Several medications can precipitate hyperkalemia when administered to patients with underlying renal insufficiency or other disturbances in potassium homeostasis. High-risk groups include patients with moderate to severe chronic renal insufficiency, hypoaldosteronism, and diseases associated with impaired response to the potassium secretory effects of aldosterone [1]. Hypoaldosteronism is often seen in elderly patients, those with chronic renal impairment or diabetic nephropathy, those with acquired immunodeficiency syndrome (AIDS), or those with primary adrenal disease [2, 3 and 4]. In addition, patients with sickle cell disease, obstructive uropathy, systemic lupus erythematosus with nephropathy, and renal transplants may have tubular resistance to the effects of mineralocorticoids [3 and 4].

Several studies have examined the incidence and cause of hyperkalemia in hospitalized patients. Depending on the definition used, hyperkalemia has been reported to develop in 1.3% (serum potassium level greater than 6.0 mEq/liter) to 10% (greater than 5.3 mEq/liter) of patients [5, 6, 7, 8, 9, 10 and 11]. Medications (Table 1 and Table 2) have been cited as a primary or contributing cause of hyperkalemia in 35% to 75% of hospitalized patients [5, 6, 7, 8, 9, 10, 11, 12, 13, 14 and 15]. Nutritional and herbal supplements, parenteral alimentation, salt substitutes, and low-sodium canned foods also contribute [12, 13, 14 and 15]. Unless otherwise mentioned, hyperkalemia is defined as a serum or plasma potassium level greater than 5.3 mEq/liter throughout this review.

Recognition of the various products that can elevate serum potassium levels and the mechanisms by which they impair potassium homeostasis is important. Cellular mechanisms ([Figure](#)) that regulate potassium handling (Na-K-ATPase pump activity, sodium channel and potassium channel function) are disturbed by these drugs and contribute to the development of hyperkalemia. In general, hyperkalemia results from three major causes: excessive potassium intake, disturbed cellular uptake of potassium, or impaired renal excretion of potassium

## Potassium input

A common cause of hyperkalemia in hospitalized patients is enteral or parenteral intake of potassium [[12](#), [13](#) and [15](#)]. Potassium administration alone, however, rarely causes hyperkalemia in the absence of an underlying defect in potassium homeostasis. For example, among 4,921 patients taking physician-prescribed potassium supplements, 179 (3.6%) developed hyperkalemia (defined as a serum potassium level above the upper limit of normal), including 13 patients who had a potassium level greater than 7.5 mEq/liter [[12](#)]. Hyperkalemia was more prevalent among older patients and those with azotemia [[12](#)]. Other studies reveal that potassium supplements cause or contribute to hyperkalemia in approximately 15% to 40% of hospitalized patients [[13](#), [14](#), [15](#) and [16](#)].

Salt substitutes are a rich source of potassium [[15](#) and [16](#)]. These products are often recommended for patients being treated with diuretics. Although the potassium content of salt alternatives is less than prescription supplements, they may cause hyperkalemia in patients with renal impairment [[15](#) and [16](#)]. Several "no-salt" substitutes contain 10 to 13 mEq of potassium per gram, a potentially dangerous potassium load [[15](#) and [16](#)]. "Low-sodium" prepared foods also contain greater amounts of potassium, because NaCl is replaced by KCl. Additionally, some nutritional supplements and herbal juices contain as much as 49 to 56 mEq of potassium per liter [[17](#)]. The urinary alkalinizing agent potassium citrate (2 mEq of potassium/mL) and packed red blood cells transfused after 10 or more days of storage (7.5 to 13 mEq of potassium/liter) can precipitate hyperkalemia in high-risk patients [[18](#) and [19](#)]. Infusion of penicillin G potassium (1.7 mEq of potassium per million units) provides another unsuspected source of potassium excess in the hospitalized patient [[20](#)]. Cardioplegia solutions can also deliver a large potassium load.

## Impaired cellular potassium homeostasis

### Beta blockers

Acute disposal of a potassium load is handled primarily by the cellular uptake of this cation, which can be impaired by some medications. Nonselective beta blockers have been associated with the development of hyperkalemia, which may rarely be severe [[21](#)].

Hyperkalemia develops by means of two different mechanisms. First, beta blockers suppress catecholamine-stimulated renin release, thereby decreasing aldosterone synthesis [21]. Second, and more importantly, nonselective beta blockers decrease cellular uptake of potassium [22]. Normally, agonist binding to the beta<sub>2</sub>-adrenergic receptor stimulates the formation of cyclic AMP, which acts through protein kinase A to phosphorylate and activate the Na-K-ATPase pump [23], leading to the influx of potassium into cells. Competitive inhibition of the beta<sub>2</sub> receptor by beta blockers decreases Na-K-ATPase function and reduces potassium uptake by cells [22, 23 and 24]. For example, three renal transplant recipients developed hyperkalemia (6.0 to 8.3 mEq/liter). This occurred within hours of treatment with intravenous labetalol, suggesting that impaired cellular uptake of potassium, rather than decreased aldosterone synthesis, was responsible [24 and 25]. Nonselective beta blockers have caused or contributed to hyperkalemia in 4% to 17% of hospitalized patients studied [5, 8, 9, 11 and 14].

### **Intravenous amino acids**

Hyperkalemia has also complicated therapy with intravenous infusions of natural (lysine, arginine) and synthetic (epsilon-aminocaproic acid) amino acids [26, 27, 28, 29, 30, 31 and 32]. A shift of potassium from the intracellular to the extracellular space in exchange for these amino acids probably underlies the development of hyperkalemia [26, 27, 28 and 29]. In intact animals, infusion of lysine caused a 1.0 to 1.5 mEq/liter increase in plasma potassium level for every 10 mEq/liter increase in plasma lysine level and led to hyperkalemia [27]. Hyperkalemia has also been described after intravenous arginine therapy in humans [28 and 29]. A mean 1.5 mEq/liter increase in serum potassium level occurred 2 hours after intravenous arginine (30 g) was administered to patients with end-stage renal disease [28]. Arginine infusion increased potassium levels above 7 mEq/liter in 2 patients with mild renal insufficiency and liver disease [29]. In these patients, serum potassium levels increased as early as 45 minutes after arginine infusion and peaked between 2 and 6 hours [28 and 29], suggesting a disturbance in cellular potassium homeostasis.

Epsilon-aminocaproic acid, which shares structural similarity with lysine and arginine, has also promoted hyperkalemia in dogs and humans [30, 31 and 32]. Improved hemostasis in patients undergoing cardiac surgery accounts for the renewed clinical importance of epsilon-aminocaproic acid in humans. We reported a patient in whom severe hyperkalemia (potassium level of 6.7 mEq/liter) developed acutely in a patient with chronic renal insufficiency treated with epsilon-aminocaproic acid (3 boluses of 10 g) to reduce perioperative blood loss [31]. A retrospective study in patients undergoing cardiac surgery revealed higher intraoperative serum potassium levels (5.9 vs 5.5 mEq/liter) in patients treated with intravenous epsilon-aminocaproic acid than in well-matched controls [32].

### **Succinylcholine**

Hyperkalemia has also been observed after infusion of succinylcholine. Depolarization of cell membranes causes a decrease in the negative interior charge of cells, reducing the

electrical barrier for potassium exit and allowing leakage of potassium out of cells [33 and 34]. Rapid induction of a cellular potassium leak with succinylcholine has been demonstrated in muscle preparations (in vitro), in intact animals, and in humans [33 and 34]. In normal subjects, the mean plasma potassium level increased by 0.5 mEq/liter within 3 to 5 minutes after intravenous succinylcholine [33]. Increases in plasma potassium levels of as much as 3.0 mEq/liter have occurred in patients with muscle trauma or neuromuscular disease [33]. In 12 patients with renal insufficiency who were treated with succinylcholine, plasma potassium levels increased by a mean of 0.7 mEq/liter in 11 of the patients and as much as 1.2 mEq/liter in 1 patient [34].

## **Digoxin**

The Na-K-ATPase pump, which transports potassium into the intracellular space, is impaired in a dose-dependent fashion by digoxin [35]. Hyperkalemia results from both impaired cellular uptake and reduced renal excretion of potassium. Digoxin does not usually lead to hyperkalemia when serum digoxin levels are therapeutic; however, overdose may cause hyperkalemia that can be fatal [35 and 36]. Rarely, hyperkalemia develops in patients who have therapeutic or mildly increased digoxin levels if other risk factors for impaired potassium handling are present [35].

## **Impaired renal potassium excretion**

### **Potassium-sparing diuretics**

Renal excretion of potassium is the major route of potassium disposal, and impairment of this process can result in clinically significant hyperkalemia. Potassium-sparing diuretics, such as amiloride, triamterene, and spironolactone, are used to enhance renal sodium losses and diminish potassium excretion in an attempt to reduce diuretic-induced hypokalemia [37]. However, these medications may also precipitate hyperkalemia in some patients. Two separate mechanisms underlie the pharmacologic actions of these diuretics, which affect the principal cells of the distal renal tubules [15]. Spironolactone, an aldosterone antagonist that competitively inhibits the binding of aldosterone to its cytoplasmic receptors, prevents nuclear uptake of the receptor and blunts potassium secretion [15 and 38]. Amiloride and triamterene diminish potassium secretion by reducing sodium reabsorption through the luminal membrane of the principal cell [37]. This results in a reduction in the electrical gradient (Figure) for potassium movement from the intracellular space to the tubular lumen, decreasing the driving force for potassium secretion.

Moderate to severe hyperkalemia has been reported in 4% to 19% of patients treated with potassium-sparing diuretics [8, 14, 15 and 38]. Treatment with triamterene and hydrochlorothiazide resulted in hyperkalemia in 26% of patients [39]. In a retrospective study, 5 patients developed hyperkalemia (9.4 to 11 mEq/liter) within 8 to 18 days of combination therapy with amiloride/hydrochlorothiazide and an angiotensin-converting enzyme (ACE) inhibitor [40]. Hyperkalemia was more common in patients with diabetes mellitus or chronic renal insufficiency. In 8 normal subjects, treatment with

spironolactone and losartan increased the mean plasma potassium level by 0.8 mEq/liter (up to 5.0 mEq/liter) and decreased mean urinary potassium excretion from 108 to 87 mEq/liter [41]. Patients with preexisting renal insufficiency or diabetes mellitus, or who are taking another medication that also impairs potassium excretion, appear to be more likely to develop hyperkalemia when treated with potassium-sparing diuretics [41, 42 and 43]. Spironolactone (300 mg daily) led to a significant elevation in plasma potassium levels in hemodialysis patients, suggesting that aldosterone may affect the cellular handling or the gastrointestinal excretion of potassium [44].

## **Nonsteroidal anti-inflammatory drugs**

Hyperkalemia is one of the many renal complications associated with nonsteroidal anti-inflammatory drugs (NSAIDs) [45]. Potassium homeostasis is impaired by NSAIDs through the inhibition of renal prostaglandin synthesis [46], especially PGE2 and PGI2. These prostaglandins stimulate renal synthesis of renin and thereby influence the subsequent synthesis of aldosterone [46]. Induction of relative hyporeninemic hypoaldosteronism is probably the major mechanism by which NSAIDs reduce renal potassium excretion and cause hyperkalemia, which was first seen with indomethacin [47]. In vitro modulation of high-conductance potassium channels in distal tubular principal cells by PGE2 and PGI2 has also been described [45 and 46]. These prostaglandins increase the number of open high-conductance potassium channels and facilitate potassium secretion. Thus, NSAIDs may interrupt renal potassium secretion by reducing the open state of these potassium channels [45 and 46]. The adverse effects of NSAIDs may be accentuated if prerenal azotemia impairs delivery of salt and water to the principal cell (Figure) in the distal nephron, further reducing potassium excretion [45 and 46].

Up to 46% of hospital patients treated with indomethacin develop an increase in serum potassium levels or hyperkalemia [48]. This adverse effect has also been seen with other NSAIDs [14, 15, 48 and 49]. The effect of the new selective cyclooxygenase-2 inhibitors on renal potassium handling is unknown. However, 3 recently reported patients had hyperkalemia (8.5 mEq/liter, 5.4 mEq/liter, and 5.1 mEq/liter) after developing acute renal failure from these drugs [50]. Preexisting hyporeninemic hypoaldosteronism and therapy with potassium-sparing diuretics and ACE inhibitors increase the risk of NSAID-associated hyperkalemia [14, 45 and 47].

## **ACE inhibitors**

ACE inhibitors commonly cause hyperkalemia by inducing a state of hypoaldosteronism [14, 51 and 52]. ACE inhibitors also impair renal potassium excretion by reducing the effective glomerular filtration rate in patients with volume depletion, renal artery stenosis, or chronic renal insufficiency. In these patients, ACE inhibitors blunt the postglomerular arteriolar constriction induced by angiotensin-II, leading to a reduction in the delivery of sodium and water to the distal nephron, which, in combination with hypoaldosteronism, may promote hyperkalemia [14, 51 and 52].

ACE inhibitors are responsible for 9% to 38% of cases of hyperkalemia in hospitalized patients [8, 11, 14 and 53]. Approximately 10% of outpatients treated with an ACE inhibitor develop hyperkalemia (greater than 6.0 mEq/liter) within a year [54]. The risk of ACE inhibitor–induced hyperkalemia appears to be proportional to the degree of renal insufficiency [8, 11, 14, 51, 52 and 53], but the serum potassium level can increase significantly in patients with only modest renal insufficiency [51, 52 and 55]. For example, high-dose captopril for 10 days induced an increase in serum potassium level, a positive cumulative potassium balance, and a reduction in both plasma and urinary aldosterone levels in 22 of 23 patients (96%) with a creatinine clearance greater than 50 mL per minute [52]. A decrease in aldosterone excretion and an increase in serum potassium level (mean increase 0.8 mEq/liter) was seen in 23 of 33 hypertensive patients (70%) after 1 week of captopril therapy [51]. All but 3 of these patients had a creatinine clearance of 60 mL per minute or more [51], and the peak serum potassium level was not predicted by the pretherapy serum creatinine level [51]. In contrast, Memon et al [53] noted a significant positive correlation of hyperkalemia with the serum creatinine level and negative correlation with creatinine clearance, emphasizing the importance of the underlying level of renal function. Reducing the ACE inhibitor dose and initiating a low-potassium diet may decrease the development of hyperkalemia in some of these patients [53 and 55], but as many as one-third of patients will require discontinuation of the medication because of ongoing hyperkalemia [53]. Combination of an ACE inhibitor with another potassium-altering medication can also precipitate hyperkalemia in patients with modest renal impairment [14, 40, 51, 52, 56, 57 and 58]. Hypoaldosteronism and depletion of effective plasma volume, such as heart failure and cirrhosis, are also important risk factors [14, 51 and 52].

### **Angiotensin-ii receptor antagonists**

Angiotensin-II receptor antagonists were recently introduced for the treatment of hypertension. Competitive binding of these drugs to the angiotensin-II receptor decreases adrenal synthesis of aldosterone. These drugs cause hyperkalemia by inducing a state of hypoaldosteronism similar to ACE inhibitors. However, it is not certain whether they cause clinically relevant hyperkalemia [59, 60, 61 and 62]. In otherwise healthy patients with essential hypertension, an angiotensin-II receptor blocker, losartan (100 mg), and an ACE inhibitor, enalapril (20 mg), had similar effects in reducing plasma aldosterone levels and 24-hour urinary aldosterone excretion [59]. Potassium homeostasis was not evaluated in this study, but the nearly identical effect of both drugs on aldosterone production suggests similar impairment of renal potassium excretion. Furthermore, data pooled from 16 double-blind clinical trials that compared losartan with ACE inhibitors demonstrated no significant difference in the development of hyperkalemia (potassium level of 5.5 mEq/liter or greater) between the two types of drugs: hyperkalemia developed in 1.5% of losartan-treated patients as compared with 1.3% of ACE inhibitor–treated patients [60]. The patients studied in these trials were healthy and at low risk to develop hyperkalemia.

There are only a few studies of angiotensin-II receptor blockers in higher risk patients. In elderly patients, losartan induced a significant increase in serum potassium levels (greater

than 0.5 mEq/liter) in 19% of patients, and hyperkalemia developed in 7% of patients [61]. Diabetic nephropathy and a serum creatinine level greater than 1.3 mg/dL were predictors of a significant increase in serum potassium level [61]. Bakris et al [62] compared the effects of lisinopril (an ACE inhibitor) with those of valsartan (an angiotensin-II receptor blocker) on serum potassium level, urinary potassium excretion, and plasma aldosterone level. After 4 weeks of therapy with lisinopril, serum potassium levels increased (by a mean of 0.2 mEq/liter), and plasma aldosterone levels and urinary potassium excretion decreased. In contrast, the valsartan group did not experience a change in serum potassium levels, plasma aldosterone levels, or urinary potassium excretion [62]. Until more data are available, it is prudent to consider angiotensin-II receptor antagonists similar to ACE inhibitors as risk factors for the development of hyperkalemia in high-risk patients.

### **Trimethoprim and pentamidine**

Patients infected with the human immunodeficiency virus (HIV) develop hyperkalemia more frequently than non-HIV-infected subjects. Treatment with trimethoprim and pentamidine are probably the major causes of this disturbance in potassium homeostasis. These drugs, which are structurally similar to amiloride, competitively inhibit sodium transport channels (Figure) in the luminal membranes of the principal cell, which indirectly inhibits potassium secretion by reducing the negative luminal charge generated by the movement of sodium out of the lumen [63]. A urine pH less than 6.0 increases the protonated form of trimethoprim, which binds the sodium channel more avidly, further decreasing renal potassium excretion [64].

The association between hyperkalemia and trimethoprim was first described in a patient with *Pneumocystis carinii* pneumonia treated with a high dose (20 mg/kg daily) of this medication [65]. A 50% incidence of mild hyperkalemia (greater than 5.0 mEq/liter) and a 10% incidence of severe hyperkalemia (greater than 6.0 mEq/liter) have been reported in HIV-infected patients treated with high-dose trimethoprim [63]. Standard-dose (360 mg daily) trimethoprim therapy in non-HIV-infected patients was associated with a 21% incidence of hyperkalemia (greater than 5.5 mEq/liter) [66]. Mild renal insufficiency was a significant risk factor for the development of higher serum potassium levels [66]. Recently, a prospective study in healthy outpatients treated with trimethoprim (360 mg/day) demonstrated that 9 of 51 patients (18%) developed a serum potassium level greater than 5.0 mEq/liter and that 3 had a serum potassium level greater than 5.5 mEq/liter [67]. Severe hyperkalemia was associated with older age, diabetes, and higher serum creatinine levels.

In a retrospective study, life-threatening hyperkalemia developed in patients who were treated with pentamidine for 6 or more days [68]. Serum potassium levels ranged from 5.1 to 8.7 mEq/liter during therapy and returned to normal upon discontinuation of pentamidine. A retrospective analysis of 32 patients with AIDS being treated with pentamidine reported a significant increase in mean serum potassium levels from 4.2 to 4.7 mEq/liter [69]. In this study, 24% of the patients developed severe hyperkalemia (greater than 5.2 mEq/liter), all of whom had renal insufficiency [69].

## Cyclosporine and tacrolimus (FK506)

Cyclosporine and tacrolimus are immunosuppressive drugs that can induce hyperkalemia in organ transplant recipients, especially in renal transplant patients, who often have an underlying disturbance in potassium excretion [14]. Cyclosporine disturbs renal potassium excretion through the induction of hypoaldosteronism [70] and may also induce a chloride channel shunt that impairs the electrochemical driving force for potassium secretion [71]. Cyclosporine and tacrolimus also reduce renal potassium excretion through a dose-dependent decrease in the activity of the basolateral Na-K-ATPase pumps (Figure) in principal cells, a process mediated by calcineurin inhibition [72 and 73]. Cyclosporine also inhibits apical secretory potassium channel activity in principal cells [74]. Finally, it can cause acute, transient hyperkalemia by increasing potassium efflux from cells [75].

Four of 35 of patients treated with cyclosporine developed hyperkalemia, as compared with none of 15 patients treated with azathioprine [70]. Twelve hyperkalemic renal transplant recipients treated with cyclosporine had a low urinary fractional excretion of potassium that did not respond to fludrocortisone [71]. Yu et al [76] noted higher serum potassium levels and lower urinary potassium excretions in 35 renal transplant recipients receiving cyclosporine as compared with matched normal controls. In another study, hyperkalemia developed in 74% of simultaneous pancreas/kidney transplant recipients and 44% of isolated kidney transplant patients treated with cyclosporine [77]. Similarly, hyperkalemia was noted in 26 of 49 pediatric heart transplant recipients (53%) who were treated with tacrolimus, most of whom had underlying impaired renal function [78]. In allogeneic blood stem cell transplant recipients, hyperkalemia (greater than 5.5 mEq/liter), often associated with renal impairment, occurred in 38% of patients treated with tacrolimus and 21% of those treated with cyclosporine [79].

## Heparin

Hyperkalemia has been described in patients treated with 5,000 units of heparin or more twice daily [80]. Low-molecular-weight heparin and heparinoids also impair potassium homeostasis [80]. Inhibition of adrenal aldosterone production by heparin underlies the reduction in renal potassium excretion and ultimately precipitates hyperkalemia. Heparin decreases the number and affinity of angiotensin-II receptors in the adrenal zona glomerulosa, reducing the main stimulus for aldosterone synthesis [80]. Heparin also directly inhibits the final enzymatic steps of aldosterone formation (18-hydroxylation), and prolonged administration in rats promotes atrophy of the zona glomerulosa [80]. Additionally, excess anticoagulation with heparin may precipitate adrenal hemorrhage and cause adrenal insufficiency [80]. Heparin increases serum potassium levels by 0.2 mEq/liter to as much as 1.7 mEq/liter among patients treated for 3 or more days [80]. Although heparin-associated hyperkalemia has been reported in normal patients, it occurs more often in patients (8% to 19%) with preexisting defects in potassium homeostasis [80].

## Conclusion

Medication-induced hyperkalemia occurs frequently in patients with altered renal function. Approximately 800,000 patients in the United States have chronic renal insufficiency (serum creatinine level greater than 2.0 mg/dL). Many patients have other disorders that impair renal potassium handling, such as diabetes mellitus with hyporeninemic hypoaldosteronism, sickle cell nephropathy, lupus nephritis, renal transplantation, and obstructive uropathy. Several commonly used drugs disrupt potassium balance in these patients and precipitate frank hyperkalemia. The high rate of polypharmacy also contributes to hyperkalemia. In addition, many patients ingest over-the-counter medications, nutritional supplements, and unknown herbal remedies in an unregulated fashion, which can further increase the risk of serious hyperkalemia. Clinicians must recognize patients at risk of hyperkalemia and avoid medications or drug combinations that may exacerbate the problem. Patients should also be educated to avoid nonprescription sources of excess potassium.

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## References

1. R.A. DeFronzo, Hyperkalemia and hyporeninemic hypoaldosteronism. *Kidney Int* **17** (1980), pp. 118–134. [Abstract-EMBASE](#) | [Abstract-MEDLINE](#) | [\\$Order Document](#)
2. M.A. Perazella and R.L. Mahnensmith, Hyperkalemia in the elderly: drugs exacerbate impaired potassium homeostasis. *J Gen Intern Med* **12** (1997), pp. 646–656. [Abstract-EMBASE](#) | [Abstract-MEDLINE](#) | [\\$Order Document](#)
3. D.C. Batlle, J.A. Arruda and N.A. Kurtzman, Hyperkalemic distal tubular acidosis associated with obstructive uropathy. *NEJM* **304** (1981), pp. 373–380. [Abstract-EMBASE](#) | [Abstract-MEDLINE](#) | [\\$Order Document](#)
4. Rastegar A, DeFronzo RA. Disorders of potassium and acid-base metabolism in association with renal disease. In: Schrier RW, Gottschalk CW, eds. *Diseases of the Kidney*. New York: Little, Brown and Company, 1997:2451–2475.
5. J. Shemer, D. Ezra, M. Modan and S. Cabili, Incidence of hyperkalemia in hospitalized patients. *Isr J Med Sci* **19** (1983), pp. 659–661. [Abstract-MEDLINE](#) | [\\$Order Document](#)
6. B. Paice, J.M.B. Gray, D. McBride and D.H. Lawson, Hyperkalemia in patients in hospital. *BMJ* **286** (1983), pp. 1189–1192. [Abstract-EMBASE](#) | [Abstract-MEDLINE](#) | [\\$Order Document](#)
7. S. Shapiro, D. Slone, G.P. Lewis and H. Jick, Fatal drug reactions among medical inpatients. *J Am Med Assoc* **216** (1971), pp. 467–472. [Abstract-MEDLINE](#) | [\\$Order Document](#)

- [8.](#) C.G. Acker, J.P. Johnson, P.M. Palevsky and A. Greenberg, Hyperkalemia in hospitalized patients. *Arch Intern Med* **158** (1998), pp. 917–924. [Abstract-EMBASE](#) | [Abstract-MEDLINE](#) | [\\$Order Document](#) | [Full Text via CrossRef](#)
- [9.](#) S. Borra, R. Shaker and M. Kleinfeld, Hyperkalemia in an adult hospitalized population. *Mt Sinai J Med* **55** (1988), pp. 226–229. [Abstract-EMBASE](#) | [Abstract-MEDLINE](#) | [\\$Order Document](#)
- [10.](#) M.L. Moore and R.R. Bailey, Hyperkalaemia in patients in hospital. *N Z Med J* **102** (1989), pp. 557–558. [Abstract-EMBASE](#) | [Abstract-MEDLINE](#) | [\\$Order Document](#)
- [11.](#) E.U. Ahmed, B.N. Mohammed, R. Matute and G.C. Burns, Etiology of hyperkalemia in hospitalized patients: an answer to Harrington’s question. *J Am Soc Nephrol* **9** (1998), p. 103A.
- [12.](#) D.H. Lawson, Adverse reactions to potassium chloride. *Q J Med* **43** (1974), pp. 433–440. [Abstract-EMBASE](#) | [Abstract-MEDLINE](#) | [\\$Order Document](#)
- [13.](#) Lawson DH, O’Connor PC, Jick H. Drug attributed alterations in potassium handling in congestive heart failure. *Eur J Clin Pharmacol.* 1982;23:21–25.
- [14.](#) J.M. Rimmer, J.F. Horn and F.J. Gennari, Hyperkalemia as a complication of drug therapy. *Arch Intern Med* **147** (1987), pp. 867–869. [Abstract-EMBASE](#) | [Abstract-MEDLINE](#) | [\\$Order Document](#)
- [15.](#) S.P. Ponce, A.E. Jennings, N.E. Madias and J.T. Harrington, Drug-induced hyperkalemia. *Medicine* **64** (1985), pp. 357–370. [Abstract-EMBASE](#) | [Abstract-MEDLINE](#) | [\\$Order Document](#)
- [16.](#) D. McCaughan, Hazards of non-prescription potassium supplements. *Lancet* **1** (1984), pp. 513–514. [Abstract](#) | [Full Text + Links](#) | [PDF \(324 K\)](#)
- [17.](#) B.A. Mueller, M.K. Scott, K.M. Sowinski and K.A. Prag, Noni juice (*Morinda citrifolia*). *Am J Kidney Dis* **35** (2000), pp. 310–312. [Abstract-EMBASE](#) | [Abstract-MEDLINE](#) | [\\$Order Document](#)
- [18.](#) J.J. Browning and K.S. Channer, Hyperkalaemic cardiac arrhythmia caused by potassium citrate mixture. *BMJ* **283** (1981), pp. 1366–1368. [Abstract-EMBASE](#) | [Abstract-MEDLINE](#) | [\\$Order Document](#)
- [19.](#) J.M. Michael, I. Dorner, D. Burns *et al.*, Potassium load in CPD-preserved whole blood and two types of packed red cells. *Transfusion* **15** (1975), pp. 144–149. [Abstract-EMBASE](#) | [Abstract-MEDLINE](#) | [\\$Order Document](#)

[20.](#) C.W. Mercer and J.R. Logic, Cardiac arrest due to hyperkalemia following intravenous penicillin administration. *Chest* **64** (1973), pp. 358–359. [Abstract-EMBASE](#) | [Abstract-MEDLINE](#) | [\\$Order Document](#)

[21.](#) P. Lundborg, The effect of adrenergic blockade on potassium concentrations in different conditions. *Acta Med Scand* **672** suppl (1983), pp. 121–132.

[22.](#) R.M. Rosa, P. Silva, J.B. Young *et al.*, Adrenergic modulation of extrarenal potassium disposal. *NEJM* **302** (1980), pp. 431–434. [Abstract-EMBASE](#) | [Abstract-MEDLINE](#) | [\\$Order Document](#)

[23.](#) H.S. Ewart and A. Klip, Hormonal regulation of the Na<sup>+</sup>-K<sup>+</sup>-ATPase: mechanisms underlying rapid and sustained changes in pump activity. *Am J Physiol* **269** (1995), pp. C295–C311. [Abstract-EMBASE](#) | [Abstract-Elsevier BIOBASE](#) | [Abstract-MEDLINE](#) | [\\$Order Document](#)

[24.](#) Y.M. Traub, M. Rabinov, J.B. Rosenfeld and S. Treuherz, Elevation of serum potassium during beta-blockade: absence of relationship to the renin–aldosterone system. *Clin Pharmacol Ther* **28** (1980), pp. 765–768. [Abstract-EMBASE](#) | [Abstract-MEDLINE](#) | [\\$Order Document](#)

[25.](#) S. Arthur and A. Greenberg, Hyperkalemia associated with intravenous labetalol therapy for acute hypertension in renal transplant recipients. *Clin Nephrol* **33** (1990), pp. 269–271. [Abstract-EMBASE](#) | [\\$Order Document](#)

[26.](#) N.G. Levinsky, I. Tyson, R.B. Miller and A.S. Relman, The relationship between amino acids and potassium in isolated rat muscle. *J Clin Invest* **41** (1962), pp. 480–487. [Abstract-MEDLINE](#) | [\\$Order Document](#)

[27.](#) H.W. Dickerman and W.G. Walker, Effect of cationic amino acids infusion on potassium metabolism in vivo. *Am J Physiol* **206** (1964), pp. 403–408. [Abstract-MEDLINE](#) | [\\$Order Document](#)

[28.](#) P. Hertz and J.A. Richardson, Arginine-induced hyperkalemia. *Arch Intern Med* **130** (1972), pp. 778–780. [Abstract-MEDLINE](#) | [\\$Order Document](#)

[29.](#) D.A. Bushinsky and F.J. Gennari, Life-threatening hyperkalemia induced by arginine. *Ann Intern Med* **89** (1978), pp. 632–634. [Abstract-EMBASE](#) | [Abstract-MEDLINE](#) | [\\$Order Document](#)

[30.](#) H.J. Carroll and D.A. Tice, The effects of epsilon aminocaproic acid upon potassium metabolism in the dog. *Metabolism* **15** (1966), pp. 449–457. [Abstract](#) | [Full Text + Links](#) | [PDF \(665 K\)](#)

- [31.](#) M.A. Perazella and P. Biswas, Acute hyperkalemia associated with intravenous epsilon-aminocaproic acid therapy. *Am J Kidney Dis* **33** (1999), pp. 782–785. [Abstract-EMBASE](#) | [Abstract-MEDLINE](#) | [\\$Order Document](#)
- [32.](#) M.A. Perazella, S. Garwood, J. Matthew *et al.*, Hyperkalemia associated with IV epsilon-aminocaproic acid. *J Am Soc Nephrol* **10**(1999), p. 123A.
- [33.](#) H.D. Weintraub, D.V. Heisterkamp and L.H. Cooperman, Changes in plasma potassium concentration after depolarizing blockers in anaesthetized man. *B J Anaesth* **41** (1969), pp. 1048–1052. [Abstract-MEDLINE](#) | [\\$Order Document](#)
- [34.](#) S.M. Yentis, Suxamethonium and hyperkalaemia. *Anaesth Intensive Care* **18** (1990), pp. 92–101. [Abstract-EMBASE](#) | [\\$Order Document](#)
- [35.](#) B. Lown, H. Black and F.D. Moore, Digitalis, electrolytes and the surgical patient. *Am J Cardiol* **6** (1960), pp. 309–337. [Abstract](#) | [Full Text + Links](#) | [PDF \(3503 K\)](#)
- [36.](#) T.W. Smith and J.T. Willerson, Suicidal and accidental digoxin ingestion. Report of five cases with serum digoxin level correlations. *Circulation* **44** (1971), pp. 29–36. [Abstract-MEDLINE](#) | [\\$Order Document](#)
- [37.](#) L.E. Ramsay, J. Hettiarachchi and R. Fraser, Amiloride, spironolactone, and potassium chloride in thiazide-treated hypertensive patients. *Clin Pharmacol* **4** (1980), pp. 533–543. [Abstract-EMBASE](#) | [Abstract-MEDLINE](#) | [\\$Order Document](#)
- [38.](#) D.J. Greenblatt and J. Koch-Weser, Adverse reactions to spironolactone. *J Am Med Assoc* **225** (1973), pp. 40–43. [Abstract-MEDLINE](#) | [\\$Order Document](#)
- [39.](#) C.J. McDonald, Dyazide and hyperkalemia. *Ann Intern Med* **84** (1976), pp. 612–613.
- [40.](#) T.F. Chiu, M.J. Bullard, J.C. Chen *et al.*, Rapid life-threatening hyperkalemia after addition of amiloride Hcl/hydrochlorothiazide to angiotensin-converting enzyme inhibitor therapy. *Ann Emerg Med* **30** (1997), pp. 612–615. [Abstract-EMBASE](#) | [Abstract-MEDLINE](#) | [\\$Order Document](#)
- [41.](#) A. Henger, P. Tutt, H.N. Hulter and R. Krapf, Acid-base effects of inhibition of aldosterone and angiotensin II action in chronic metabolic acidosis in humans. *J Am Soc Nephrol* **10** (1999), p. 121A.
- [42.](#) D.A. Feinfeld and C.P. Carvounis, Fatal hyperkalemia and hyperchloremic acidosis. Association with spironolactone in the absence of renal impairment. *J Am Med Assoc*. **240** (1978), p. 1516. [Abstract-EMBASE](#) | [Abstract-MEDLINE](#) | [\\$Order Document](#)
- [43.](#) J.L. McNay and E. Oran, Possible predisposition of diabetic patients to hyperkalemia following administration of potassium-retaining diuretics, amiloride (MK-870). *Metabolism* **19** (1970), pp. 58–70. [Abstract](#) | [Full Text + Links](#) | [PDF \(906 K\)](#)

- [44.](#) M. Papadimitriou, A. Vyzantiadis, A. Milionis, D. Memmos and P. Metaxas, The effect of spironolactone in hypertensive patients on regular haemodialysis and after renal allotransplantation. *Life Support Systems* **1** (1983), pp. 197–206.
- [45.](#) D. Schlondorff, Renal complications of nonsteroidal anti-inflammatory drugs. *Kidney Int* **44** (1993), pp. 643–653. [Abstract-EMBASE](#) | [Abstract-MEDLINE](#) | [\\$Order Document](#)
- [46.](#) S. Garella and R.A. Matarese, Renal effects of prostaglandins and clinical adverse effects of nonsteroidal anti-inflammatory agents. *Medicine* **63** (1984), pp. 165–181. [Abstract-EMBASE](#) | [Abstract-MEDLINE](#) | [\\$Order Document](#)
- [47.](#) S.Y. Tan, R. Shapiro, R. Franco *et al.*, Indomethacin-induced prostaglandin inhibition with hyperkalemia. *Ann Intern Med* **90** (1979), pp. 783–785. [Abstract-EMBASE](#) | [Abstract-MEDLINE](#) | [\\$Order Document](#)
- [48.](#) A. Zimran, M. Kramer, M. Plaskin *et al.*, Incidence of hyperkalaemia induced by indomethacin in a hospital population. *BMJ* **291** (1985), pp. 107–108. [Abstract-EMBASE](#) | [Abstract-MEDLINE](#) | [\\$Order Document](#)
- [49.](#) R.P. Kimberly, R.E. Bowden, H.R. Keiser *et al.*, Reduction of renal function by newer non-steroidal antiinflammatory drugs. *Am J Med* **64** (1978), pp. 804–806.
- [50.](#) M.A. Perazella and J. Eras, Are selective COX-2 inhibitors nephrotoxic?. *Am J Kidney Dis* **35** (2000), pp. 937–940. [Abstract-EMBASE](#) | [Abstract-MEDLINE](#) | [\\$Order Document](#)
- [51.](#) S.C. Textor, E.L. Bravo, F.M. Fouad *et al.*, Hyperkalemia in azotemic patients during angiotensin-converting enzyme inhibition and aldosterone reduction with captopril. *Am J Med* **73** (1982), pp. 719–725. [Abstract](#) | [Full Text + Links](#) | [PDF \(913 K\)](#)
- [52.](#) S.A. Atlas, D.B. Case, J.E. Sealey *et al.*, Interruption of the renin–angiotensin system in hypertensive patients by captopril induces sustained reduction in aldosterone secretion, potassium retention and natriuresis. *Hypertension* **1** (1979), pp. 274–280. [Abstract-MEDLINE](#) | [\\$Order Document](#)
- [53.](#) A. Memon, M. Siddiqui, M. Agraharkar and T. Ahuja, Incidence and predictors of hyperkalemia in patients with chronic renal failure on angiotensin converting enzyme inhibitors. *J Am Soc Nephrol* **10** (1999), p. 294A.
- [54.](#) L.C. Reardon and D.S. Macpherson, Hyperkalemia in outpatients using angiotensin-converting enzyme inhibitors. *Arch Intern Med* **158** (1998), pp. 26–32. [Abstract-MEDLINE](#) | [\\$Order Document](#) | [Full Text via CrossRef](#)

- [55.](#) T. Keilani, F.R. Danesh, W.A. Schlueter *et al.*, A subpressor low dose of ramipril lowers urinary protein excretion without increasing plasma potassium. *Am J Kidney Dis* **33** (1999), pp. 450–457. [Abstract-EMBASE](#) | [Abstract-MEDLINE](#) | [\\$Order Document](#)
- [56.](#) J.E. Heeg, P.E. deJong, R. Vriesendorp and D. deZeeuw, Additive antiproteinuric effect of the NSAID indomethacin and the ACE inhibitor lisinopril. *Am J Nephrol* **10** (1990), pp. 94–97. [Abstract-EMBASE](#) | [Abstract-MEDLINE](#) | [\\$Order Document](#)
- [57.](#) U. Dahlstrom and E. Karlsson, Captopril and spironolactone therapy for refractory congestive heart failure. *Am J Cardiol* **71** (1993), p. 29A. [Abstract-EMBASE](#) | [Abstract-MEDLINE](#) | [\\$Order Document](#)
- [58.](#) T. Hannedouche, P. Landais, B. Goldfarb *et al.*, Randomised controlled trial of enalapril and beta-blockers in non-diabetic chronic renal failure. *BMJ* **309** (1994), pp. 833–837. [Abstract-EMBASE](#) | [Abstract-MEDLINE](#) | [\\$Order Document](#)
- [59.](#) M.R. Goldberg, T.E. Bradstreet, E.J. McWilliams *et al.*, Biochemical effects of losartan, a nonpeptide angiotensin II receptor antagonist, on the renin–angiotensin–aldosterone system in hypertensive patients. *Hypertension* **25** (1995), pp. 37–46. [Abstract-EMBASE](#) | [Abstract-MEDLINE](#) | [\\$Order Document](#)
- [60.](#) A.I. Goldberg, M.C. Dunlay and C.S. Sweet, 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* **75** (1995), pp. 793–795. [SummaryPlus](#) | [Full Text + Links](#) | [PDF \(378 K\)](#)
- [61.](#) A. Savoy, C.E. Palant, G. Patchin and W.F. Graettinger, Losartan effects on serum potassium in an elderly population. *J Am Soc Nephrol* **9** (1998), p. 111A.
- [62.](#) G.L. Bakris, M. Siomas, W.K. Bolton *et al.*, Differential effects of valsartan and lisinopril on potassium homeostasis in hypertensive patients with nephropathy. *J Am Soc Nephrol* **10** (1999), p. 68A.
- [63.](#) H. Velázquez, M.A. Perazella, F.S. Wright and D.H. Ellison, Renal mechanism of trimethoprim-induced hyperkalemia. *Ann Intern Med* **119** (1993), pp. 296–301. [Abstract-EMBASE](#) | [Abstract-MEDLINE](#) | [\\$Order Document](#)
- [64.](#) M. Schreiber, L.E. Schlanger, C.B. Chen *et al.*, Antikaliuretic action of trimethoprim is minimized by raising urine pH. *Kidney Int* **49** (1996), pp. 82–87. [Abstract-EMBASE](#) | [Abstract-MEDLINE](#) | [\\$Order Document](#)
- [65.](#) A.M. Kaufman, G. Hellman and R.G. Abramson, Renal salt wasting and metabolic acidosis with trimethoprim-sulfamethoxazole therapy. *Mt Sinai J Med* **50** (1983), pp. 238–239. [Abstract-EMBASE](#) | [Abstract-MEDLINE](#) | [\\$Order Document](#)

- [66.](#) R. Alappan, M.A. Perazella and G.K. Buller, Hyperkalemia in hospitalized patients treated with trimethoprim-sulfamethoxazole. *Ann Intern Med* **124** (1996), pp. 316–320. [Abstract-EMBASE](#) | [Abstract-MEDLINE](#) | [\\$Order Document](#)
- [67.](#) R. Alappan, G.K. Buller and M.A. Perazella, Trimethoprim-sulfamethoxazole therapy in outpatients: is hyperkalemia a significant problem. *Am J Nephrol* **19** (1999), pp. 389–394. [Abstract-EMBASE](#) | [Abstract-MEDLINE](#) | [\\$Order Document](#) | [Full Text via CrossRef](#)
- [68.](#) M. Lachaal and R.C. Venuto, Nephrotoxicity and hyperkalemia in patients with acquired immunodeficiency syndrome treated with pentamidine. *Am J Med* **87** (1989), pp. 260–263. [Abstract](#) | [Full Text + Links](#) | [PDF \(449 K\)](#)
- [69.](#) L.L. Briceland and G.R. Bailie, Pentamidine-associated nephrotoxicity and hyperkalemia in patients with AIDS. *DICP* **25** (1991), pp. 1171–1175.
- [70.](#) P. Heering and B. Grabanese, Influence of cyclosporine A on renal tubular function after kidney transplantation. *Nephron* **59** (1991), pp. 66–70. [Abstract-EMBASE](#) | [Abstract-MEDLINE](#) | [\\$Order Document](#)
- [71.](#) K.S. Kamel, J.H. Ethier, S. Quaggin *et al.*, Studies to determine the basis for hyperkalemia in recipients of a renal transplant who are treated with cyclosporine. *J Am Soc Nephrol* **2** (1992), pp. 1279–1284. [Abstract-MEDLINE](#) | [\\$Order Document](#)
- [72.](#) J.A. Tumlin and J.M. Sands, Nephron segment-specific inhibition of Na<sup>+</sup>/K<sup>+</sup>-ATPase activity by cyclosporin A. *Kidney Int* **43** (1993), pp. 246–251. [Abstract-EMBASE](#) | [Abstract-MEDLINE](#) | [\\$Order Document](#)
- [73.](#) J.P. Lea, J.M. Sands, S.J. McMahon and J.A. Tumlin, Evidence that the inhibition of Na<sup>+</sup>/K<sup>+</sup>-ATPase activity by FK506 involves calcineurin. *Kidney Int* **46** (1994), pp. 647–652. [Abstract-EMBASE](#) | [Abstract-MEDLINE](#) | [\\$Order Document](#)
- [74.](#) B.N. Ling and D.C. Eaton, Cyclosporin A inhibits apical secretory K<sup>+</sup> channels in rabbit cortical collecting tubule principal cells. *Kidney Int* **44** (1993), pp. 974–984. [Abstract-EMBASE](#) | [Abstract-MEDLINE](#) | [\\$Order Document](#)
- [75.](#) Y. Pei, R. Richardson, C. Greenwood, M. Math, P.Y. Wong and A. Baines, Extrarenal effect of cyclosporine A on potassium homeostasis in renal transplant recipients. *Am J Kidney Dis* **22** (1993), pp. 314–319. [Abstract-EMBASE](#) | [Abstract-MEDLINE](#) | [\\$Order Document](#)
- [76.](#) H.S. Yu, H.S. Chang, D.J. Han *et al.*, Change of transtubular potassium gradient (TTKG) in renal transplant recipients. *J Am Soc Nephrol* **10** (1999), p. 14A.
- [77.](#) B. Kaplan, Z. Wang, M.M. Abecassis *et al.*, Frequency of hyperkalemia of simultaneous pancreas and kidney transplants with bladder drainage. *Transplantation* **62**

(1996), pp. 1174–1175. [Abstract-EMBASE](#) | [Abstract-Elsevier BIOBASE](#) | [Abstract-MEDLINE](#) | [\\$Order Document](#)

[78.](#) A. Assante-Korang, G.J. Boyle, S.A. Webber *et al.*, Experience of FK506 immune suppression in pediatric heart transplantation: a study of long term adverse effects. *J Heart Lung Transplant* **15** (1996), pp. 415–422.

[79.](#) M. Woo, D. Przepiorka, C. Ippoliti *et al.*, Toxicities of tacrolimus and cyclosporin A after allogeneic blood stem cell transplantation. *Bone Marrow Transplant* **20** (1997), pp. 1095–1098. [Abstract-EMBASE](#) | [Abstract-MEDLINE](#) | [\\$Order Document](#)

[80.](#) J.R. Oster, I. Singer and L.M. Fishman, Heparin-induced aldosterone suppression and hyperkalemia. *Am J Med* **98** (1995), pp. 575–586. [Abstract](#) | [PDF \(1013 K\)](#)



Table 1. Medications That Commonly Cause Hyperkalemia\* [legend](#)

| Medication              | Reported Percentage of Patients Who Develop Hyperkalemia from the Drug | Reported Percentage of M |
|-------------------------|--|--------------------------|
| Potassium supplements   | 3–24   |                          |
| Beta blockers           | 1–5  |                          |
| Digoxin                 | 2–15   |                          |
| Potassium-sparing drugs | 2–19   |                          |
| NSAIDs                  | 10–46  |                          |
| ACE inhibitors          | 10–38  |                          |
| Angiotensin-II blockers | 2–7  |                          |
| Trimethoprim            | 6–21   |                          |
| Pentamidine             | 5–24   |                          |
| Cyclosporine            | 11–44  |                          |
| Tacrolimus              | 15–53  |                          |
| Heparin                 | 8–17   |                          |



Table 2. Medications That Can Cause Hyperkalemia and Their Mechanism of Action [legend](#)

| Medication   | Mechanism   |
|--|---|
| <b>Increased potassium input</b>   |   |
| <b>Potassium supplements and salt substitutes</b>                                | <b>Potassium ingestion</b>  |
| <b>Nutritional and herbal supplements</b>  | <b>Potassium ingestion</b>  |
| <b>Stored packed red blood cells</b>   | <b>Potassium infusion</b>   |
| <b>Penicillin G potassium</b>  | <b>Potassium ingestion</b>  |
| <b>Transcellular potassium shifts</b>  |   |
| <b>Beta blockers</b>   | <b>Decrease beta-2-driven potassium uptake</b>  |
| <b>Intravenous amino acids (lysine, arginine, and epsilon-aminocaproic acid)</b> | <b>Release of potassium from cells</b>  |
| <b>Succinylcholine</b>   | <b>Depolarize cell membranes</b>  |
| <b>Digoxin intoxication</b>  | <b>Decrease Na<sup>+</sup>-K<sup>+</sup>-ATPase activity</b>  |
| <b>Impaired renal excretion</b>  |   |
| <b>Potassium-sparing diuretics</b>   |   |
| <b>Spirolactone</b>  | <b>Aldosterone antagonism</b>   |
| <b>Triamterene</b>   | <b>Block Na<sup>+</sup> channels in principal cells</b>   |
| <b>Amiloride</b>   | <b>Block Na<sup>+</sup> channels in principal cells</b>   |
| <b>Nonsteroidal anti-inflammatory drugs</b>                                      | <b>Decrease aldosterone synthesis Decrease renal blood flow and glomerular filtration</b>                               |
| <b>ACE inhibitors and angiotensin-II receptor blockers</b>                       | <b>Decrease aldosterone synthesis Decrease renal blood flow and glomerular filtration</b>                               |
| <b>Trimethoprim and pentamidine</b>  | <b>Block Na<sup>+</sup> channels in principal cells</b>   |
| <b>Cyclosporine and tacrolimus (FK506)</b>                                       | <b>Decrease aldosterone synthesis Decrease Na-K-ATPase activity Decrease renal blood flow and glomerular filtration</b> |
| <b>Heparin</b>   | <b>Decrease aldosterone synthesis</b>   |