CHAPTER 63

Aldosterone Antagonists, Amiloride, and Triamterene

Chopra Tushar and Mark Douglas Okusa

OBJECTIVES

This chapter will:

1. Review the structure, mechanism of action, and biologic effects of aldosterone antagonists, amiloride, and triamterene (the potassium-sparing diuretics).
2. Contrast the properties of the potassium-sparing diuretics with other diuretic drugs.
3. Discuss the renal and extrarenal effects of aldosterone antagonism.
4. Review the use of aldosterone antagonists, amiloride, and triamterene in clinical practice.

A class of diuretic drugs that act primarily in the cortical collecting tubule is referred to as potassium-sparing diuretics and comprises three pharmacologically distinct groups: aldosterone antagonists (spironolactone), pteridines (triamterene), and pyrazinoylguanidines (amiloride, Table 63.1). They are different from the thiazides and loop diuretics, which cause kaliuresis. As a group, the potassium-sparing diuretics are relatively weak diuretics, but their distinctly different site and mechanism of action may result in an increase in serum potassium and mild metabolic acidosis. Diuretic activity is weak because of the late distal location of the cortical collecting tubule, in which fractional sodium reabsorption usually does not exceed 3% of the filtered

TABLE 63.1

Comparisons of the Potassium-Sparing Diuretics

PROPERTY	SPIRONOLACTONE	EPLERENONE	AMILORIDE	TRIAMTERENE
Class/action	Mineralocorticoid and androgen receptor antagonist	Selective mineralocorticoid receptor antagonist	Inhibition of amiloride-sensitive sodium channels in the distal convoluted tubule (DCT) and collecting ducts	Inhibition of Na^+-K^+-$2Cl^-$ cotransporter in the DCT and collecting ducts
Absorption	Readily absorbed; absorption increased with food	Probably well absorbed	Readily absorbed	Readily absorbed
Onset and duration of effect	Days	Days	Hours	Hours
Protein binding (%)	90	50	23	67
Metabolism	Liver	Liver	Not metabolized	Liver
Active metabolites?	Yes	No	No	Yes
Route of excretion (in order of importance)	Renal	Renal	Renal	Renal
Bile-feces	Bile-feces	Bile-feces	Bile-feces	
Usual starting dose	25 mg twice daily	25 mg daily	2.5–5.0 mg twice daily	50 mg daily
Usual maintenance dose	25–100 mg twice daily	50 mg daily	5–10 mg twice daily	50–100 mg twice daily

Data from Wishart DS, Knox C, Guo AC, et al. DrugBank: A comprehensive resource for in silico drug discovery and exploration. *Nucleic Acids Res.* 2006;34:D668–D672; Caswell A, Harvey A, Bellantonio J, eds. eMIMS. Available at http://mims.hcn.net.au/; Barnes BJ, Howard PA. Eplerenone: A selective aldosterone receptor antagonist for patients with heart failure. *Ann Pharmacother.* 2005;39:68–76.

BOX 63.1

Indications for Collecting Duct Diuretics

A. Ascites secondary to cirrhosis (MR antagonist)
B. Lithium-induced diabetes insipidus (amiloride with thiazide)
C. Prevention of hypokalemia (owing to potassium-wasting diuretics)
D. Prevention of hypomagnesemia (owing to potassium-wasting diuretics)
E. Diuretic resistance (used in combination with other diuretics)
F. Familial hypertension syndromes
   1. Familial hyperaldosteronism type II (MR antagonist)
   2. Glucocorticoid resistance, primary cortisol resistance (MR antagonist)
   3. Liddle syndrome (amiloride/triamterene)
   4. Apparent mineralocorticoid excess, 11β-hydroxysteroid dehydrogenase type II deficiency (MR antagonist)
   5. Activating MR mutation, Geller syndrome, MR_{L810} (amiloride)

MR, Mineralocorticoid receptor.

load. They often are used in combination with thiazide or loop diuretics to enhance natriuresis yet restrict potassium loss (Box 63.1). They are also first-line drugs in the treatment of edema from cirrhosis as well as familial hypertension syndromes (see Box 63.1).

ALDOSTERONE ANTAGONISTS

Aldosterone is a steroid hormone secreted by the zona glomerulosa of the adrenal cortex. It binds to the mineralocorticoid receptor within the cytoplasm of tubular epithelium. The ligand-receptor complex translocates into the cell nucleus, where it modulates the expression of a variety of genes (aldosterone-induced proteins, or AIPs). Aldosterone regulates expression of the apical membrane Na^+ channel (ENaC), apical membrane K^+ channel (ROMK), basolateral Na^+,K^+-ATPase and Na^+/H^+ exchange (NHE) isoforms of the late distal convoluted tubule, connecting tubule, and collecting duct. These effects are mediated in part by the aldosterone-stimulated transcription of the gene encoding the serum/glucocorticoid-induced kinase-1 (SGK-1). The kinase then becomes activated in the cell by phosphorylation and mediates increased transporter activity by direct and indirect mechanisms. For example, the activity of ENaC is increased by SGK-1–mediated phosphorylation of Nedd4-2, a protein that promotes recycling of ENaC from the plasma membrane. Phosphorylated Nedd4-2 has impaired interactions with ENaC leading to increased number of these channels in the membrane and increased Na reabsorption. There are also long-term changes in cell morphology caused by aldosterone, an increase in area of the basolateral membrane.[1,2] In the distal convoluted tubule, SGK-1 phosphorylates WNK4 and Nedd4-2, which diminishes their inhibitory effects on sodium-chloride cotransporter (NCC).[3] This results in active sodium (and hence water) reabsorption from, and potassium excretion into, the urine. Net effects of aldosterone therefore include sodium retention, potassium excretion, and an overall expansion of the extracellular fluid volume.

Nonrenal sites of aldosterone-mediated sodium and potassium exchange are of minor clinical significance but include other epithelialized tissues, such as the salivary glands and gastrointestinal tract. Aldosterone synthesis in the adrenal cortex is regulated mainly by angiotensin II, serum potassium, and, to a lesser extent, serum sodium and adrenocorticotrophic hormone. Circulating plasma concentrations of aldosterone are elevated markedly through neurohormonal processes associated with congestive heart failure and contribute to the perpetuation of cardiovascular injury.[1] It is also increasingly appreciated that aldosterone has important actions beyond the kidney and ion transport, including increasing reactive oxygen species and inflammatory process, which leads to fibrosis in heart, vasculature, kidney tubulointerstitium, and glomerulus.[3–6] The known pathologic effects attributable to aldosterone excess continue

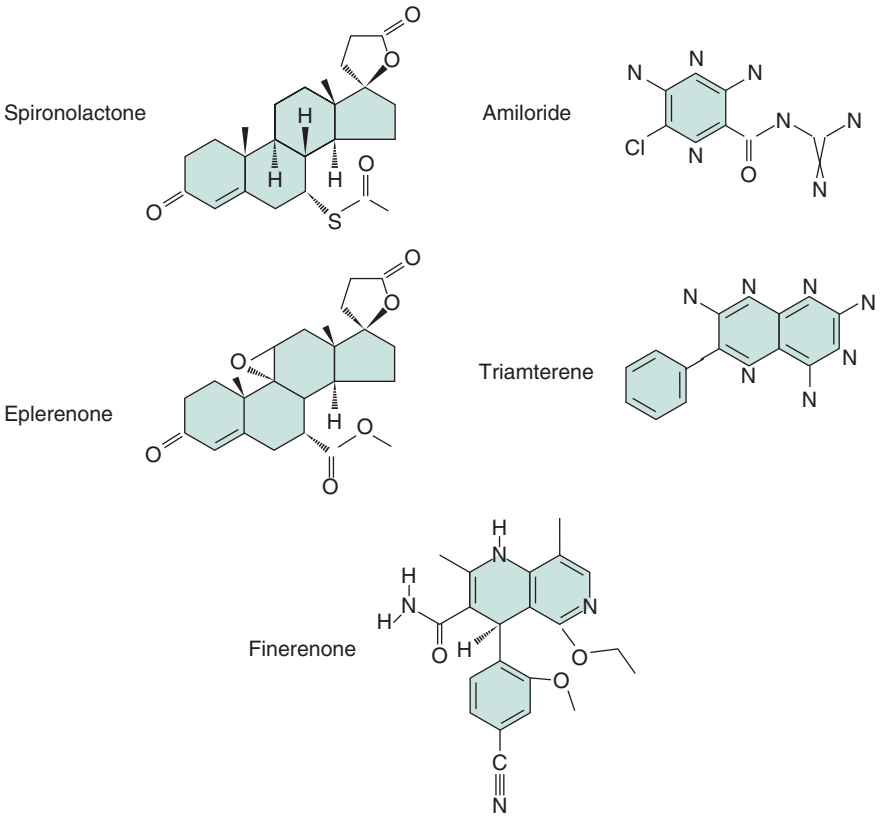

FIGURE 63.1 Structure of potassium-sparing diuretics.

to accumulate; currently they include atherosclerosis, cardiac fibrosis, endothelial dysfunction, arrhythmias, and cardiac hypertrophy.[3,7]

Although the renin-angiotensin-aldosterone system has been previously regarded as a salt-, blood pressure–, and fluid-regulating system centered on the kidney, it is increasingly appreciated that some or all of the constituents of the system are synthesized in vascular structures such as the heart and in vessel walls, where concentrations can greatly exceed circulating levels.[8] In addition, the mineralocorticoid receptor sites have been identified in nonepithelial cells such as cardiomyocytes, endothelial cells, vascular smooth muscles, adipocytes, and monocytes.[3,7] Mineralocorticoid receptor–independent effects of aldosterone occur via angiotensin-II receptors as well as G protein-coupled receptor 30.[3] This situation, in part, explains why the full effects of aldosterone blockade on the cardiovascular system cannot be completely explained solely through its effect on the renal tubule. The renal effects of aldosterone antagonists may not manifest for several days, and full cardiovascular effects may take weeks. Several drugs of varying specificity have been developed to interfere with aldosterone's binding at the mineralocorticoid receptor within renal tissue and at other sites.

Spironolactone

Spironolactone, a synthetic 17-lactone steroid aldosterone antagonist introduced in 1959, enters the target cell from the peritubular side and competitively binds at the mineralocorticoid receptor (Fig. 63.1). The spironolactone-mineralocorticoid complex is excluded from the nucleus and inhibits production of Na^+,K^+-ATPase, effectively reducing the number of Na^+ pumps present on the interstitial side of target tubular epithelial cells. Impeding the action of aldosterone thus causes renal retention of potassium, excretion of sodium (natriuresis), and modestly increased urine volume (diuresis). Secondarily, there is a tendency to increased urinary chloride and calcium excretion and for retained magnesium and hydrogen ions. Although mineralocorticoid antagonism has been shown to produce sustained increases in plasma renin and serum aldosterone levels that are consistent with interference with the negative regulatory feedback of aldosterone on renin secretion, these changes do not overcome the effects of spironolactone on the kidney. Spironolactone also has moderate antiandrogenic effects owing to its antagonistic binding at peripheral androgen receptors and inhibition of ovarian testosterone synthesis.[9]

Spironolactone is well absorbed from the gastrointestinal tract, especially when coadministered with food, and undergoes rapid and extensive metabolism. Its mainly sulfur-containing active metabolites are bound to plasma proteins and undergo predominantly renal excretion. Approximately a quarter of the administered dose is metabolized to canrenone, which also exerts significant mineralocorticoid receptor blockade and antiandrogenic effects. Adverse effects attributable to spironolactone can be predicted largely from its mode of action. Hyperkalemia is a potentially serious problem that is especially likely to occur in patients who have impaired renal function or are receiving other drugs that can raise serum potassium levels. Although spironolactone would be expected to accumulate in patients with significant hepatic dysfunction, dose reduction is not generally necessary in such patients.

The antiandrogenic properties of spironolactone, although exploited in the treatment of conditions involving androgen excess, also can have undesirable effects, particularly in men, who may experience gynecomastia and sexual dysfunction.

An obvious clinical role for spironolactone is primary hyperaldosteronism (Conn syndrome), in which unregulated aldosterone excess results in potassium depletion, hypertension, and expansion of the extracellular fluid volume. Consistent with its mechanism of action, spironolactone appears effective and well tolerated for this disorder and can be used as preoperative therapy for the patient with a secreting adenoma or as medical therapy for such a patient in whom surgery is inappropriate.[10] Another long-standing use for spironolactone is in medical management of patients with ascites because of chronic liver disease. In this clinical situation, spironolactone as a single agent or in combination with loop diuretics has been demonstrated to be more effective and better tolerated than other regimens.[11] The antiandrogenic properties of spironolactone have been used as first-line treatment for hirsutism, in which it is as effective as cyproterone acetate and flutamide.[12] Combination therapy incorporating spironolactone and another of these hormonal therapies is common practice for idiopathic hirsutism.

The most common use for spironolactone, however, is in treatment of cardiac failure, for which it has become established therapy as an adjunct to other agents, such as angiotensin-converting enzyme (ACE) inhibitors, loop diuretics, and beta blockers. Spironolactone's major use previously had been to counteract the kaliuretic action of loop and thiazide diuretics, which are frequently used as first-line therapy for cardiac failure and hypertension. The widespread use of ACE inhibitors as standard therapy for cardiac failure also contributed to past low use of aldosterone antagonists, which was based on concerns (that subsequently have been validated) about the potential for serious hyperkalemia. Cumulative evidence for the cardiovascular benefits of mineralocorticoid receptor blockade, however, has resulted in a significant resurgence in the use of spironolactone.[13] The administration of relatively low doses of spironolactone (25 mg daily) has been demonstrated to improve symptoms and reduce mortality for patients with severe left ventricular systolic dysfunction who are already receiving loop diuretics and ACE inhibitors.[14] It is likely that several mechanisms contribute to these cardioprotective effects. Although predicted effects mediated through renal mechanisms include improved blood pressure control and resolution of edema, significant natriuresis is not achieved universally. The evidence that the nonrenal actions of spironolactone are extremely important is compelling. Through extrarenal mineralocorticoid receptor antagonism, spironolactone appears to halt and reverse cardiac fibrosis and remodeling as well as possibly exerting direct and indirect antiarrhythmic effects.[14,15]

Although spironolactone therapy is associated with considerable cardioprotective benefit, it is clear that close monitoring to detect and prevent serious complications is extremely important. The significant rise in spironolactone use in patients with heart disease has been followed closely by major increases in morbidity and mortality secondary to hyperkalemia.[13] The impact of this problem, although perhaps foreseeable given the drug's mechanism of action, was not predicted by the results of preceding studies and reflects a number of crucial differences between patients receiving drug therapy in the context of a clinical trial and those managed in the broader context of day-to-day clinical practice. Therefore the importance of giving careful consideration to comorbid medical conditions (such as renal impairment, especially diabetic nephropathy), coadministered drugs (particularly ACE inhibitors, angiotensin II blockers, nonsteroidal antiinflammatory drugs, and potassium supplements), and drug dosing is readily apparent. Recommended doses vary from 50 to 200 mg per day, along with regular monitoring of serum electrolyte values. The level of renal dysfunction at which the risks of dangerous hyperkalemia outweigh the cardioprotective benefits of spironolactone is not clear. Avoiding spironolactone therapy in patients with serum creatinine values greater than 221 μmol/L is prudent, because patients with poorer renal function were excluded by the major study in which benefit was demonstrated.[14] Such an approach cannot completely prevent hyperkalemia, however, which can still occur in patients with more normal renal function.[16] Baseline potassium measurement should be undertaken in all patients; a serum potassium concentration greater than 5 mmol/L is a contraindication to the use of spironolactone. Vigilant monitoring and downward dose adjustment are advised for the use of this agent in patients with serum potassium levels exceeding 5.5 mmol/L.

Renin angiotensin system blockade, through the use of angiotensin-converting enzyme inhibitors (ACEI) and/or angiotensin receptor blockers (ARB) has been shown to delay the progression of kidney disease. Not surprisingly, in preclinical studies, aldosterone antagonists have shown to be effective in the treatment of progressive kidney disease. However, despite the beneficial effects in animal studies, large long-term studies of their use in patients with renal disease are lacking. Most short-term studies using surrogate endpoints have shown that aldosterone antagonists reduce blood pressure and proteinuria. The role of aldosterone antagonists as an add-on therapy to preexisting ACEI and/or ARB has been studied in several clinical trials in the past decade. A recent Cochrane database and systematic review identified 27 studies with 1549 patients that studied the effect of aldosterone antagonists alone or in combination with renin-angiotensin system blockade in patients with CKD. There was no information on major cardiovascular events, mortality, and progression to end-stage renal disease as patient level outcomes. Spironolactone combined with ACEI or ARB (or both) significantly reduced proteinuria. Systolic and diastolic blood pressure were reduced significantly at the end of treatment with spironolactone. However, spironolactone increased the risk of hyperkalemia.[17]

The role of aldosterone antagonists in treating resistant hypertension is established. The Pathway-2 trial aimed to test the hypothesis that resistant hypertension is caused most often by excessive sodium retention and that spironolactone would be superior to nondiuretic add-on drugs. In this double-blinded, placebo-controlled, crossover trial of 335 patients with resistant hypertension, patients received spironolactone, bisoprolol, or doxazosin. Spironolactone was more effective in lowering blood pressure in those with lower baseline renin levels.[18]

Aldosterone antagonism has been studied in ESRD patients, but most studies are limited by a small power and do not address patient-related outcomes such as major cardiovascular events, mortality, and progression to end-stage renal disease.

Ito et al. assessed left ventricular mass index in an open-labeled prospective randomized trial of 158 patients on peritoneal dialysis treated with spironolactone as an add-on therapy to ACE-inhibitor or ARB for 2 years. There was a significant improvement in the rate of change of left ventricular mass index in patients taking spironolactone compared with the control group. Adverse events such as

hyperkalemia were noted in three patients.[19] A large scaled, multicenter, double-blinded randomized controlled trials such as the ALCHEMIST (aldosterone antagonist chronic hemodialysis intervention no survival trial) is underway to recruit 825 patients.[35]

In summary, the use of aldosterone antagonists reduced blood pressure as well as proteinuria in patients with CKD, but whether they attenuate the risk of progression to ESRD or risk of serious cardiovascular events is not known.[17] Because of the potential for serious toxicity and the lack of definitive data in patients with CKD or ESRD, these agents should not be used routinely in this population.

EPLERENONE

The incidence of undesirable effects relating to spironolactone's antiandrogenic properties leads to discontinuation of this agent in a significant number of patients. Painful breast enlargement and erectile dysfunction in men are particularly common complaints, even with relatively low doses. Eplerenone is substantially more specific to the mineralocorticoid receptor than spironolactone, with a chemical structure that differs by replacement of the 17-α thioacetyl group with a carboxymethoxy group (see Fig. 63.1). Although it is a competitive antagonist of the mineralocorticoid receptor, eplerenone binds only very weakly to androgen, glucocorticoid, and progesterone receptors and is therefore essentially devoid of the feminizing side effects characteristic of spironolactone.[20] Other important differences of eplerenone from spironolactone are a lack of active metabolites, only modest protein binding, and a lack of change in bioavailability when administered with food.

Because eplerenone is metabolized via the hepatic CYP3A4 pathway, its potential for drug interactions is increased. Demonstrable beneficial effects of eplerenone in patients with cardiac failure after myocardial infarction are similar to those of spironolactone, including significantly better mortality and hospitalization outcomes.[21] To date, no study comparing the effectiveness of eplerenone and spironolactone has been conducted. Given that the mode of action of eplerenone is essentially identical to that of spironolactone (aside from antiandrogenic effects), the same mechanisms leading to benefit would be expected. The side effects associated with androgen blockade, however, are substantially lower in patients taking eplerenone, and rates of discontinuation of therapy resulting from such side effects are the same as those for placebo. As with spironolactone, the tendency to hyperkalemia in patients taking eplerenone is a serious problem mandating close supervision as long as therapy continues. Dosing recommendations suggest commencing at a dose of 25 mg daily, increasing to a maximal target dose of 50 mg daily (if tolerated) within 4 weeks. Baseline evaluation of renal function is useful to assess the potential for hazardous hyperkalemia. Patients with baseline serum creatinine concentrations greater than 221 mmol/L were excluded from the largest clinical trial of eplerenone, and a creatinine clearance less than 50 mL/min was found to confer a significant risk of elevated serum potassium concentration.[21] Regular monitoring is important with eplerenone therapy, even in patients with apparently preserved renal function, and dose reduction should occur with serum potassium levels exceeding 5.5 mmol/L. Also, eplerenone treatment reduces combined end point of death and hospitalization in patients with systolic dysfunction and mild symptoms.[22]

Finerenone

Finerenone is a third-generation nonsteroidal mineralocorticoid receptor antagonist with stronger mineralocorticoid receptor-binding potential compared with spironolactone and eplerenone. It is cleared predominantly by CYP3A4 (90%) and CYP2C8 (10%) compared with renal clearance. Heinig et al. evaluated PK parameters for finerenone in 32 patients divided into normal renal function (CrCl > 80), mild (CrCl 50–80), moderate (30–50), and severe (CrCl < 30) renal impairment. The absorption time was similar in all groups of approximately 30 to 60 min. The renal function had no consistent effect on maximum serum concentration (Cmax) but mean exposure (AUC) to finerenone was similar for normal and mild renal impairment but higher in severe renal impairment. The terminal elimination half-life (t½) was 2.23 hours in normal renal function, 2.34 in mild, 2.88 in moderate, and 3 hours for severe renal function. The unbound fraction was unchanged at 10.6% across all four renal function groups. Protein binding is moderate to high and therefore with changes in serum albumin may increase the exposure to total and unbound finerenone. Renal excretion played a greater role in the elimination of metabolites, but because these metabolites are inactive they are not anticipated to have any clinical implications.[23]

Finerenone has been used in Phase III clinical trials for the treatment of patients with diabetic kidney disease and for reducing the risk of cardiovascular events in patients with diabetic kidney disease. The safety and efficacy of different doses of finerenone were tested in a randomized controlled trial in patients with diabetes and albuminuria. Finerenone demonstrated a dose-dependent reduction in urine albumin to creatinine ratio (UACR) and low rates of hyperkalemia.[25]

In a randomized controlled study comparing finerenone to eplerenone in patients with congestive heart failure and type 2 DM and CKD (eGFR > 30 in type 2 DM and 30–60 in a patient without type 2 DM). Overall, patients in the finerenone 10- to 20-mg dose had the greatest reduction of composite outcome, including death from any cause, cardiovascular hospitalization, or emergency presentation to hospital compared with eplerenone.[25]

NONALDOSTERONE ANTAGONIST POTASSIUM-SPARING DIURETICS

Nonaldosterone antagonist potassium-sparing diuretics have net effects on renal electrolyte handling very similar to those of the mineralocorticoid antagonists, but their mechanisms of action are distinct. Epithelial sodium channel (ENaC) blockers are a class of diuretics called amiloride and triamterene.

Amiloride

Amiloride hydrochloride, a pyrazine-carbonyl-guanidine, is chemically unrelated to other known diuretics (see Fig. 63.1). By binding to sodium channels in the distal convoluted tubule and collecting ducts, amiloride inhibits sodium reabsorption, producing a mild natriuresis and diuresis. Sodium channel blockade also leads to a decrease in the net negative potential of the tubular lumen, reducing the secretion of potassium and hydrogen ions into the urine.[26]

Compared with thiazides and loop diuretics, amiloride is therefore potassium sparing and may be used to offset potential kaliuresis in patients taking these more potent potassium-wasting diuretics. Improved adherence to therapy may be achieved through fixed-dose combination preparations, which incorporate thiazide diuretics, as treatment for conditions leading to edema and for ascites and hypertension. Amiloride is absorbed readily from the gastrointestinal tract and is excreted predominantly unchanged by the kidneys. It does not undergo any hepatic metabolism. Recommended dose ranges from 2.5 to 5.0 mg daily. Monitoring of serum electrolyte values and careful assessment for additional factors that could potentiate hyperkalemia are important.

Triamterene

Triamterene is a potassium-sparing, weak diuretic with a mode of action similar to that of amiloride. Through inhibition of the Na^+-K^+-$2Cl^-$ cotransporter, triamterene reduces sodium reabsorption from the tubule, creating an electrical potential difference unfavorable to passive excretion of potassium by the distal tubule. This agent often is used in combination with thiazides and loop diuretics to reduce urinary potassium and magnesium losses and so obviates the need for supplementation of these electrolytes.[27] Triamterene is metabolized mainly to the sulfate conjugate hydroxy-triamterene, which possesses activity similar to that of the parent drug. Patients with significant liver dysfunction are at risk for drug accumulation owing to increased bioavailability from alterations in first-pass metabolism and decreased clearance. Apart from hyperkalemia, adverse effects relating to triamterene include triamterene-containing renal calculi.[28] Recommended dosing for triamterene ranges from 50 to 100 mg up to twice daily. Triamterene is much less potent and more toxic. It is associated with kidney stone, crystalluria, or cylinduria.[29]

Clinical Use and Implications of Potassium-Sparing Diuretics

ENaC are highly Na^+ selective channels that are blocked by the diuretics amiloride and triamterene. ENaC is composed of three structurally related subunits, referred to as α, β, and γ. The gain of function mutations is seen in Liddle syndrome, and loss of function mutation is seen in pseudohypoaldosteronism.

Aldosterone and urine flow activate ENaC and renal K+ secretion.[30] Proteases and sheer stress also have a fundamental role in regulating ENaC. Proteases activate ENaC by cleaving the α or γ subunits at defined sites.[31] Proteases activate sodium channels by removing the inhibitory fragments.[32] The extent of ENaC proteolysis is a major determinant of channel activity.

There is evidence that nephrotic urine (containing plasmin, a serine protease) activates ENaC expressed in mouse collecting ducts. Plasminogen filtered in nephrotic urine is activated to plasmin by the renal tubular urokinase-type plasminogen activator.[33] These experiments suggest a hypothesis that renal ENaC is aberrantly activated in nephrotic rats, thus providing a rationale for the use of an ENaC inhibitor to enhance renal sodium excretion.[33]

Drugs that can inhibit ENaC include trimethoprim.[34] Trimethoprim at higher doses of 320 mg/day would result in hyperkalemia. The risk is amplified in patients with renal insufficiency, increased potassium intake, and concomitant use of renin-angiotensin system blockers.

CONCLUSION

Aldosterone antagonists, amiloride, and triamterene have a distinctive niche role in clinical practice because of their specific effects on electrolyte handling. Their potassium-sparing properties make them useful adjunct therapies to more potent diuretic drugs given for edema and hypertension. The aldosterone antagonists spironolactone and eplerenone also have an important role as components of cardiac failure management, partly by virtue of their extrarenal beneficial cardiovascular effects. The safe use of these agents, however, requires consideration of factors that may contribute to hyperkalemia and careful monitoring of serum electrolyte values.

Key Points

1. The potassium-sparing diuretics act via mechanisms in the renal tubule that are distinct from those of other diuretic agents.
2. These unique properties result in biologic effects specific to drugs within the class that can be complementary to other diuretics, especially kaliuretic agents such as loop diuretics and thiazides.
3. These agents may be useful therapies for hypertension and clinical disorders causing edema.
4. The aldosterone antagonists have clinically important cardioprotective effects in patients with cardiac failure mediated via renal and nonrenal mechanisms.
5. Consistent with their effect on renal tubule electrolyte handling, the potassium-sparing diuretics can cause hyperkalemia, especially in patients with renal impairment or during coadministration of other agents that can lead to elevations in serum potassium concentration (e.g., ACE inhibitors, angiotensin II blockers).

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A complete reference list can be found online at ExpertConsult.com.

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