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DIURETICS (thiazide, loop, potassium sparing): A Review

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Abstract— *Diuretics are the class of drugs that mainly act by increasing the urine output promoting the excretion of salts, excess water and other toxic substances out of the body. Diuretic drug therapy is mainly used to lower the blood pressure and in treatment of various diseases related to kidney, heart or liver problems. Thiazide type of diuretics is the most commonly prescribed that act on distal convulated tubules. Loop diuretics (furosemide , torsemide) act by preventing Na+ reabsorption . Triamterene and Amiloride , potassium sparing diuretics lowers blood pressure and treat edema conditions in patients eliminating excess water level. All type of diuretics are used in cases of hypertension, liver cirrhosis, heart failure and water poisoning(edema).*

Keywords— ***diuretics, thiazide diuretics, furosemide, amiloride.***

I. INTRODUCTION

Diuretics, characterized as medications that enhance the elimination of water and sodium in urine (resulting in a natriuretic effect), possess a variety of mechanisms of action, enabling their combination use. Each diuretic impacts sodium reabsorption across all segments of the nephron, including the proximal tubule, the loop of Henle, the distal tubule, and the collecting tubule.(1)

Over the past forty years, various categories of diuretics have emerged as the preferred therapeutic approach for a wide range of cardiovascular and non-cardiovascular conditions. Diuretics constitute the primary course of action for managing mild hypertension, with thiazide-type diuretics being designated as one of the equally recommended first-line treatment choices, alongside beta-blockers, calcium antagonists, and angiotensin-converting enzyme inhibitors/angiotensin receptor blockers.(2)

II. MECHANISM OF ACTION OF DIURETICS

Diuretics constitute a diverse array of medications, but some generalizations can be made. Apart from mannitol and vasopressin receptor antagonists, all diuretics primarily function by inhibiting sodium reabsorption at various points along the renal tubules. The pathway for organic acid secretion delivers carbonic anhydrase inhibitors, loop diuretics, thiazide diuretics, and thiazide-like diuretics into the tubular lumen, reaching their sites of action. In contrast, aldosterone antagonists reach their site of action, the principal cells of the cortical collecting duct, via the bloodstream.

Acetazolamide, a carbonic anhydrase inhibitor, disrupts the reabsorption of Na+, HCO3−, and water, thereby increasing the delivery of Na+ to the distal collecting duct and causing K+ loss.

Loop diuretics like furosemide, torasemide, azosemide, and bumetanide act on the thick ascending limb of the loop of Henle, where 20% to 30% of filtered NaCl is reabsorbed. They bind to the Na-K-2Cl transport protein,

inhibiting its action, which impairs the reabsorption of Na+, K+, and Cl–, leading to increased Na+ delivery to the distal tubule. This, in turn, promotes K+ secretion into the distal tubule and reduces the kidney's osmotic driving force and concentrating ability.

Thiazide and related diuretics primarily act on the distal convoluted tubule, where they block the NaCl cotransporter, resulting in reduced Na+ and Cl– reabsorption. This increases the delivery of Na+ to collecting ducts, enhances the exchange of Na+ and K+, and causes K+ wasting. Thiazides also affect the kidney's diluting capacity and Mg+ reabsorption but stimulate Ca2+ reabsorption, which is beneficial in treating calcium-containing renal stones. They lower blood pressure by decreasing peripheral resistance through an unknown mechanism. Initially, they decrease extracellular volume (ECF) and cardiac output, but ECF gradually returns to near normal over several weeks to months.

Potassium-sparing diuretics, acting at the cortical collecting duct, can be divided into two subcategories. Pteridine analogs (such as triamterene and amiloride) inhibit reabsorption by the epithelial Na+ channel (ENaC) of the collecting duct. These drugs do not result in appreciable diuresis or significant antihypertensive efficacy as monotherapies but are often used with other agents to correct K+ deficiency. Aldosterone receptor blockers act in the cytoplasm of principal cells to downregulate the basolateral Na+/K+ pump and the aldosterone-sensitive ENaC. Both subcategories impair Na+ reabsorption and decrease H+ and K+ secretion, which would otherwise occur due to voltage changes across the membrane.

Mannitol, an osmotic diuretic, exerts its effect along the entire length of the renal tubule regardless of hydration status, impairing normal tubular water reabsorption. Ultimately, mannitol disrupts the medullary solute gradient and impairs the kidney's concentrating ability. Like thiazide and loop diuretics, it increases Na+ delivery to the distal nephron, leading to K+ loss.

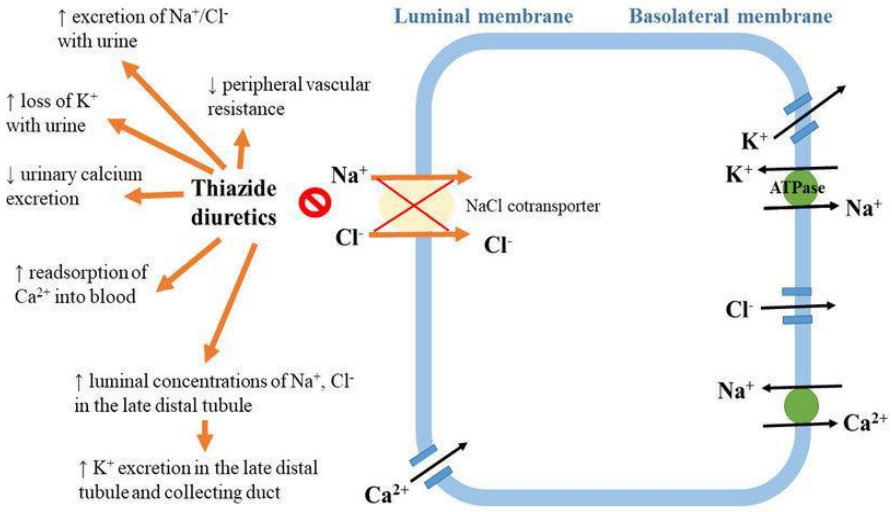
Vasopressin receptor antagonists block vasopressin at V2 receptors, preventing free water reabsorption at the collecting ducts, and thereby increasing free water excretion.(3)

III. THIAZIDE DIURETICS

As derivatives of 1,2,4-benzothiadiazine-1,1-dioxide, thiazides are more accurately classified as benzothiadiazines. Variations in substitutions and heterocyclic rings exist among different compounds, but they all share an unsubstituted sulfonamide group, akin to carbonic anhydrase inhibitors. Although they retain some capacity to inhibit carbonic anhydrase, their diuretic effect is not solely reliant on this activity. At physiological pH, thiazides function as organic anions and necessitate active secretion into the proximal tubule lumen via a renal organic anion transporter due to their high protein binding and limited glomerular filtration. Uric acid competes with thiazides for secretion into the proximal tubule, potentially leading to hyperuricemia and triggering gout in susceptible individuals.

The primary mechanism by which thiazide diuretics achieve their blood pressure-lowering effects is through inhibition of the electroneutral sodium chloride transporter, present in the apical membrane of the early segment of the distal tubule. By impeding sodium reabsorption at this site, the delivery of sodium to the collecting duct is augmented, fostering natriuresis and enhancing exchange with potassium and magnesium, both of which can also become depleted.(4)

The anti-proteinuric impacts of thiazide-like diuretics – like chlorthalidone and indapamide – have undergone scrutiny. A preliminary 12-week investigation examined the effects of chlorthalidone in 12 patients with moderate to advanced CKD, revealing a 40–45% reduction in albuminuria. However, patients encountered a simultaneous elevation in serum creatinine by week 8, attributed to volume depletion, followed by gradual improvement and return to baseline by week 12. This transient surge in serum creatinine coincided with a decrease in total body weight and an elevation in renin and aldosterone levels(5). Comparable outcomes have been noted in the kidney transplant population, with a noted 30% reduction in proteinuria and mitigation of peripheral edema, albeit with a temporary deterioration in kidney function, which could complicate the assessment of potential rejection(6). Indapamide has likewise exhibited the capacity to diminish albuminuria alone or when combined with RAS blockade in diabetic patients with persistent albuminuria.(7-10)



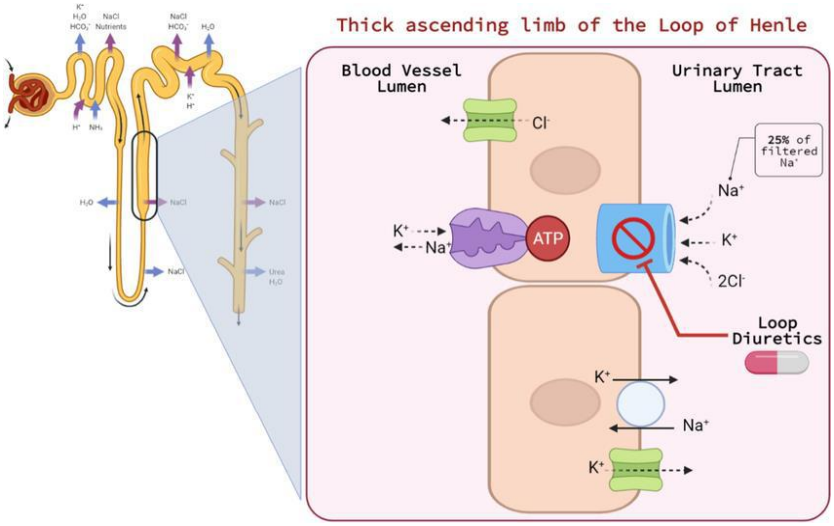
IV. LOOP DIURETICS

Loop diuretics enhance urinary sodium excretion in the loop of Henle by inhibiting the sodium-potassium-chloride cotransporter 2(11). Insights from small randomized controlled trials (RCTs) with short follow-up durations suggest that loop diuretics might ameliorate signs and symptoms of fluid retention in heart failure patients(12-15)

Loop diuretics function by inhibiting a substantial portion of Na+ reabsorption while targeting the thick ascending limb of the loop of Henle. This characteristic gives rise to their classification as loop diuretics. They are recognized as the most potent diuretics.(16)

In individuals with kidney failure, loop diuretics are commonly administered in the form of repeated doses of furosemide, one or two doses of torsemide, or a single dose of metolazone per day. Their primary utilization in heart failure (HF), chronic kidney disease (CKD), and cirrhosis stems from their ability to facilitate the elimination of sodium and water.

In cases of hypertensive crisis accompanied by fluid overload, or when intestinal absorption of the drug is compromised (such as in patients with HF and reduced intestinal perfusion), intravenous administration of furosemide or torsemide may be employed.(17)



V. POTASSIUM SPARING DIURETICS

Potassium-sparing diuretics prove beneficial in managing resistant hypertension and salt-sensitive forms of hypertension, prevalent among black, obese, diabetic, and elderly patients.(18) This category encompasses Mineralocorticoid Receptor (MR) antagonists (such as Spironolactone and Eplerenone)

and Epithelial sodium transport channel blockers like Amiloride and Triamterene.(19)

The interference of a drug's effects by concurrent administration of other drugs, herbs, supplements, or food is termed drug interaction.(20-21).Potassium-sparing diuretics carry the risk of inducing hyperkalemia. Aldosterone antagonists reduce potassium secretion by inhibiting the binding of aldosterone to its cytoplasmic receptors, while Epithelial sodium transport channel blockers decrease potassium secretion by reducing sodium reabsorption.(22) Hyperkalemia, an electrolyte imbalance, is associated with cardiac arrhythmias such as ventricular fibrillation and asystole, muscle weakness, paralysis, and sudden cardiac death. (23)

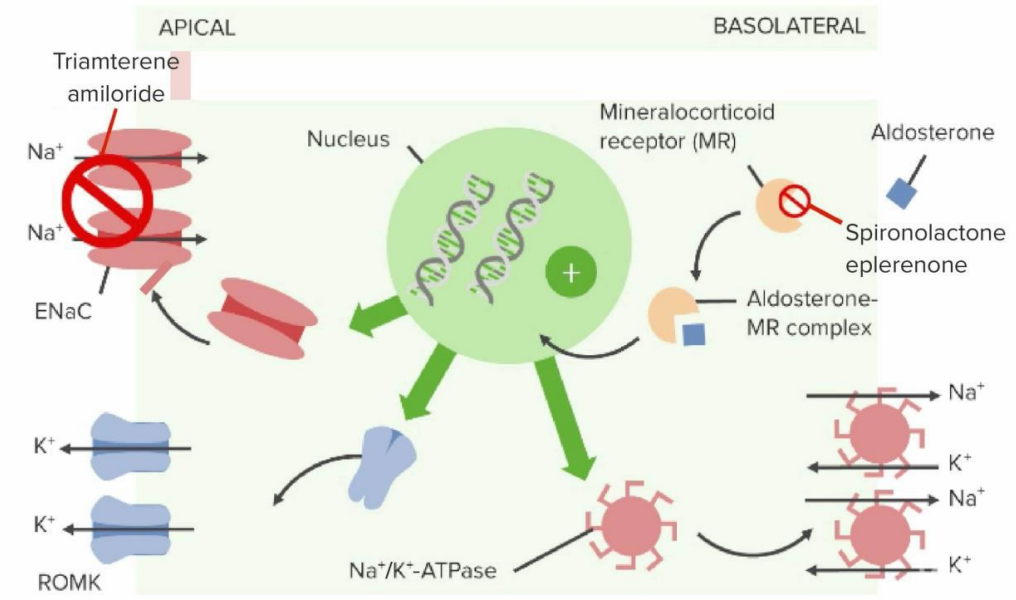
Amiloride, a potassium-sparing diuretic, exhibits greater potassium-sparing activity than diuretic effects. It belongs to the pyrazinoylguanidine derivative class.

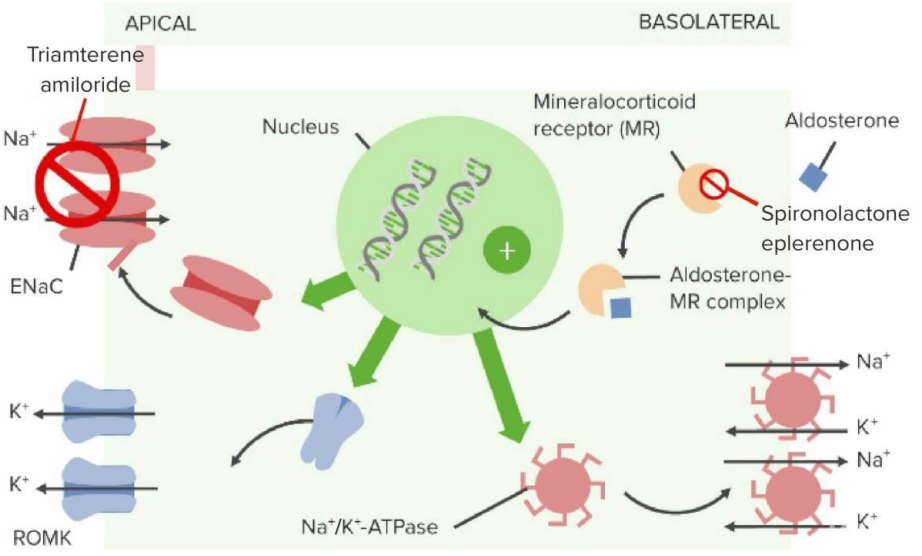
FDA indications include adjunctive use with thiazides (or other kaliuretic agents) for managing chronic heart failure or uncomplicated essential hypertension to:

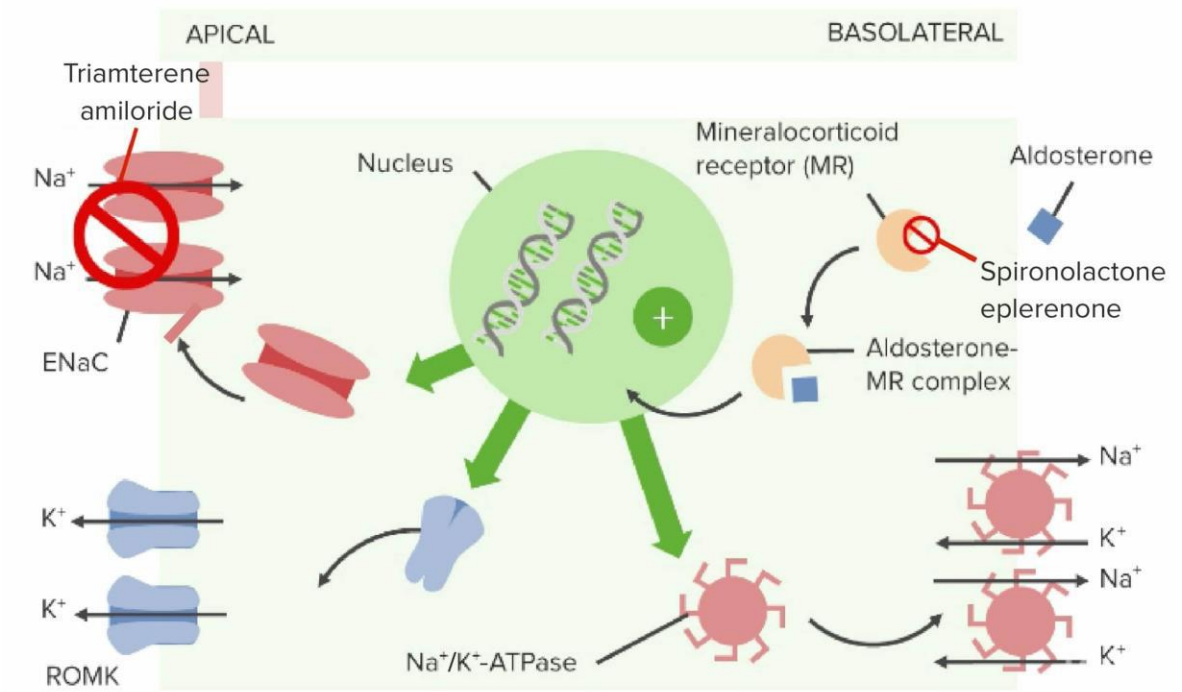
Assist in restoring normal serum potassium levels in individuals experiencing hypokalemia due to kaliuretic therapy.

Prevent hypokalemia in patients prone to significant complications from its occurrence.

Amiloride may also find utility in off-label indications such as Liddle syndrome, thiazolidinediones-induced edema, lithium-induced polyuria, cystic fibrosis, insulin-induced edema, and multiple myeloma. (25-28)







VI. OTHERS

Other antihypertensive medications also demonstrated positive outcomes. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) were linked to a reduced risk of Alzheimer's dementia. These findings align with our results, suggesting that potassium plays a significant role in cognitive well-being, as both ACE inhibitors and ARBs elevate serum potassium levels. Nonetheless, ACE inhibitors and ARBs might possess a distinctive protective mechanism related to inhibiting the renin-angiotensin-aldosterone system. Beta-blockers also showed benefits, likely attributable to their blood pressure-lowering effect, which shields against cerebral vascular damage. Among calcium channel blockers, dihydropyridine (DHP) agents exhibited greater protective effects compared to non-DHP blockers. However, it remains uncertain whether these medications possess a distinct mechanism for safeguarding neurocognitive health beyond their antihypertensive action.(29)

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