WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 11, Issue 1, 276-285. Review Article ISSN 2277– 7105

DIURETIC FOR HYPERTENSION: A REVIEW

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Article Received on
24 October 2021,

Revised on 14 Nov. 2021,
Accepted on 04 Dec. 2021

DOI: 10.20959/wjpr20221-22528

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ABSTRACT

Antihypertensive drugs comprise several classes of compound with the therapeutic intention of preventing, controlling, or treating hypertension. The classes of antihypertensive drug differ both structurally and functionally. Diuretics, in one form or another, have been around for centuries and this review summarizes the key features of the most commonly used diuretics. This review and update focuses on the clinical features of Thiazide diuretics, loop diuretics and osmotic diuretics agent. Diuretics are the second most commonly prescribed class of antihypertensive medication, and thiazide-related diuretics have increased at a rate greater than that of antihypertensive medications as a whole. Compared to other classes of medications, thiazide diuretics are atleast as effective in reducing cardiovascular events (CVEs) in patients with hypertension and are more effective than b-blockers and angiotensin converting enzyme inhibitors in reducing strok Diuretics, in particular low dose thiazide and thiazide-like diuretics, are widely used in the treatment of hypertension. They have excellent outcome data and high safety and low side effects profiles. In this article, the physiology, pharmacological actions, side effects, use of diuretics in hypertension are reviewed. In addition, the effective use of diuretics in the management of hypertension is discussed.

KEYWORDS: Thiazide diuretics, loop diuretics, potassium-sparing diuretics, hypertension, Role of diuretics.

INTRODUCTION

Hypertension (high blood pressure) is a frequent disorder in which the blood's long-term force against the artery walls is high enough to produce health problems such as heart disease. The word diuretic comes from the Greek words diu (through) oyr1ih (to urinate), and it refers to any chemical that enhances urine flow and thus water excretion.[1] The majority of diuretics work by lowering sodium chloride reabsorption at various sites in the nephron (Figure 1), resulting in an increase in urine sodium and, as a result, water loss. Diuretics are a class of medications used to change the volume and/or composition of body fluids in a variety of clinical circumstances, including hypertension and edematous states including acute and chronic heart failure, nephrotic syndrome, acute and chronic renal illness, and liver cirrhosis.[2–3] They work by reducing sodium chloride reabsorption at various locations in the nephron, resulting in increased sodium chloride excretion and water loss in the urine. Thiazide and thiazide-type diuretics have been the mainstay of antihypertensive therapy for more than 40 years and are still used quite widely in the treatment of hypertension. Patients with renal failure or severe heart failure may benefit from diuretics like furosemide, which block sodium transport in the Henle loop.[4] The potassium-sparing (retaining) medicines, which comprise epithelial sodium channel blockers (such as amiloride and triamterene) and aldosterone receptor blockers, are the third type of diuretic used to treat hypertension.

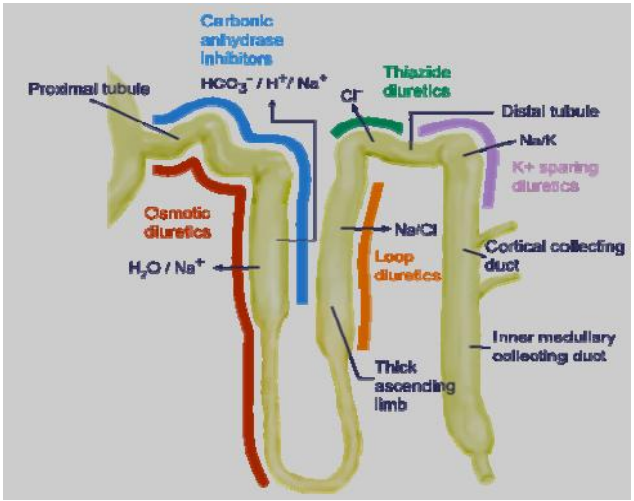


Fig 1: Site of action of different diuretic class on the Nephron.

HOW DIURETIC WORKS

Most diuretics work by lowering salt reabsorption in the renal tubules, lowering the luminal-cellular osmotic gradient, which limits water absorption and causes diuresis. All of the transporters that diuretic drugs inhibit reside on the luminal surface of the tubule, with the

exception of spironolactone and its analogue, therefore the diuretic agents must physically 'get there' to block the symport or uniport transporter.[5] This means they must be secreted into the tubular fluid and arrive in sufficient quantity at their intended destination to be beneficial. The mechanism involves facilitated diffusion and secretion into the tubular fluid via the organic acid pathway in the proximal tubule in the case of loop diuretics, thiazides, and the carbonic anhydrase inhibitor acetazolamide, all of which are acidic. Organic bases like amiloride and triamterene enter the tubular lumen via the organic base secretory process, which also occurs in the proximal tubule. Spironolactone and other aldosterone antagonists work through a cytosolic receptor and are therefore transported to their target location through the blood and the basolateral membrane. Glomerular filtration is reduced if the diuretic is heavily protein bound (.96 percent). Even in hypoalbuminuria, there isn't enough 'free' medication to get across at any given time. Other factors come into play as well, and these will be looked at apart from the diuretic or disease that affects it.

Osmotic diuretic

Osmotic diuretics are substances that are filtered at the glomerulus but not completely reabsorbed. Mannitol and glucose are two examples (when glucose has exceeded its maximum reabsorption capacity). Glucose is reabsorbed through a saturable sodium linked receptor. As a result, when the filtered load of glucose surpasses the proximal tubule's glucose transport maximum, glucose becomes a non-reabsorbable osmotically active particle. The osmotic gradient for water reabsorption is decreased by this increase in osmotic activity. Osmotic diuretics decrease NaCl reabsorption in the proximal tubule and thick ascending limb of Henle due to their effects on tubular fluid osmolality. The net result is that osmotic diuretics are potent diuretics which lead to increased excretion of water and NaCl.[6]

Site of action

The proximal convoluted tubule and the descending limb of the Loop of Henle are where osmotic diuretics exert the most effect. Water can freely pass through these areas. They also counteract ADH's function in the collecting tubule via osmotic effects.

Mechanism of action

Filtered mannitol is sufficiently concentrated to reduce tubular fluid reabsorption. Continuous Na+ reabsorption provides an osmotic gradient that allows reabsorbed Na+ to flow back into the tubule. K+ secretion is stimulated by increased distal flow. Mannitol prevents urine

concentration by increasing total renal and medullary blood flow and decreasing the medullary solute gradient.[7-8] Shown In fig -2.

Adverse effect

hyponatremia and hypochloremia. hyperkalemic acidosis.

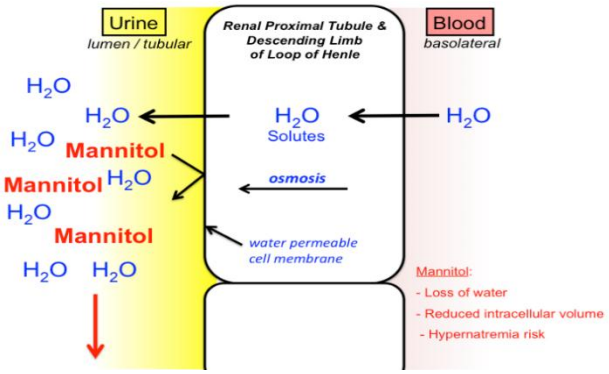


Fig. 2: Mechanism of osmotic diuretic.

Carbonic anhydrase inhibitors

Carbonic anhydrase inhibitors (acetazolamide) stop carbonic acid from breaking down normally, reducing bicarbonate absorption. Because the NaH antiporter is also involved in NaCl reabsorption, these drugs also prevent NaCl absorption in the proximal tubule. The osmotic gradient for water reabsorption is reduced when salt reabsorption is reduced. This causes the proximal tubule to transfer more NaHCO3, NaCl, and water to the remaining nephron. Because the thick ascending limb of Henle is well adapted to managing an increased load of NaCl, a large portion of the increased NaCl administration is reabsorbed there. The rest of the nephron is not geared for bulk reabsorption of NaHCO3. The net result is moderate increase in sodium and bicarbonate in the urine along with an increase in urinary flow rate (water excretion).

Site of action

Carbonic anhydrase inhibitors (CAIs) act primarily in the proximal tubule; an additional, albeit modest, effect along the distal nephron is also observed.

Mechanism of action

CAIs cause an alkaline diuresis with impaired reabsorption of Na+, Cl, and HCO3 and decreased excretion of titratable acid and NH4+ by inhibiting luminal and cellular carbonic anhydrase. Although hypokalemia is uncommon, there is significant kaliuresis. Distal Na+

and HCO3 reabsorption, as well as the development of metabolic acidosis, limit diuretic efficacy by limiting the filtered load to HCO3, hence limiting natriuresis. Carbonic anhydrase activity is present in most diuretics.[9-10] Shown in fig 3.

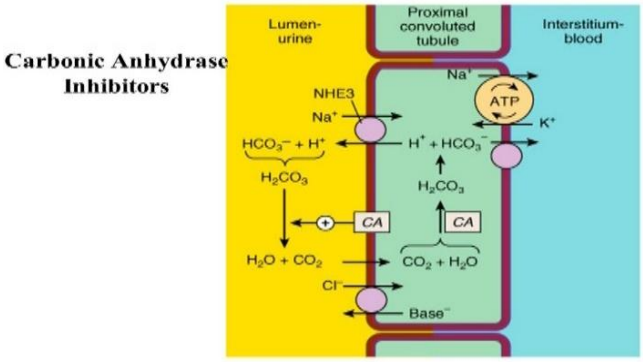


Fig. 3: Mechanism of carbonic unhydrase inhibitors.

Loop diuretic

To reach its site of action, the thick ascending limb of Henle, loop diuretics must enter the tubular fluid. The luminal receptor, which is responsible for the reabsorption of 1 sodium, 1 potassium, and 2 chloride ions, is blocked by these diuretics. Loop diuretics are very strong diuretics because the thick ascending limb is responsible for around 20% of salt chloride reabsorption. They cause more salt, potassium,chloride, and water to be excreted.[11]

Site of action

The thick ascending limb of Henle's loop

Mechanism of action

The mechanism of action for loop diuretics like furosemide is by inhibiting the apical sodium/potassium/chloride transporter in the thick ascending limb of the loop of Henle.[11] shown in fig 4.

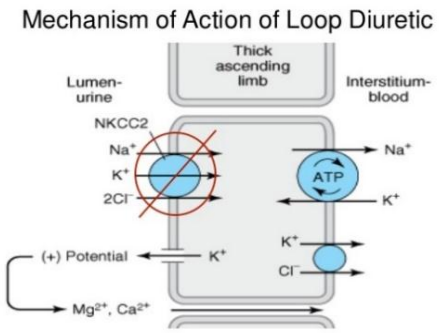


Fig. 4: Mechanism of Loop diuretic.

Thiazide Diuretics (Hydrochlorothiazide)

To reach their target in the early distal convoluted tubule, these diuretics must first penetrate the tubular fluid. The luminal receptor, which serves as an electroneutral sodium chloride transporter, is blocked by these diuretics.[12] Thiazide diuretics have a moderate potency since the distal convoluted tubule is responsible for about 5% of total salt chloride reabsorption. They cause more salt, potassium, chloride, and water to be excreted.

Site of action

Thiazide diuretics control hypertension in part by inhibiting reabsorption of sodium (Na^+) and chloride (Cl^-) ions from the distal convoluted tubules in the kidneys by blocking the thiazide-sensitive Na^+-Cl^- symporter.

Mechanism of action

Calcium reabsorption at the distal tubule is increased by thiazide diuretics. Thiazides indirectly increase the activity of the basolateral Na+/Ca2+ antiporter to maintain intracellular Na+ levels by lowering sodium concentration in tubule epithelial cells, allowing Ca2+ to exit the epithelial cells and enter the renal interstitium. As a result, the intracellular Ca2+ concentration falls, allowing additional Ca2+ from the tubule lumen to enter epithelial cells via apical Ca2+-selective channels (TRPV5). In other words, when there is less Ca2+ in the cell, the driving power for reabsorption from the lumen increases.

Thiazides are also hypothesised to boost Ca2+ reabsorption through a mechanism that involves sodium and calcium reabsorption in the proximal tubule in response to sodium deprivation. Part of this response is due to increased parathyroid hormone action.[13-14] shown in fig 5.

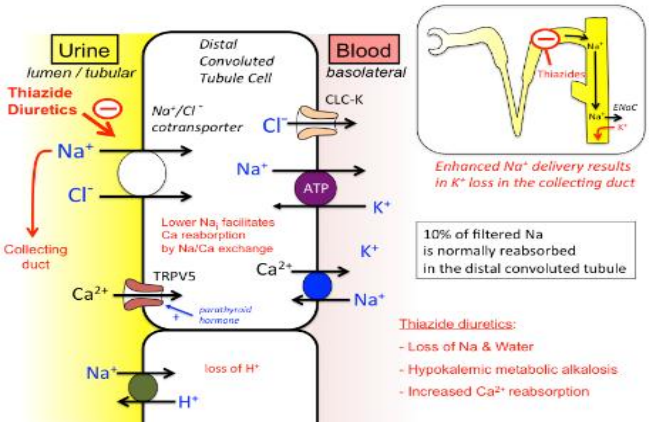


Fig. 5: Mechanism of Thiazide diuretic.

Diuretics acting in the Collecting Duct

These drugs work by either blocking the sodium channel in the luminal membrane (amiloride) or acting as competitive antagonists to aldosterone's cytoplasmic effects (spironolactone). Either of these actions will result in a slight increase in sodium excretion in the end. Because less sodium is reabsorbed in the collecting duct, the lumen has a lower negative potential, resulting in decreased potassium and hydrogen ion release. As a result, unlike diuretics that operate before the collecting duct, these diuretics cause potassium secretion to decrease**.**

Site of action

Potassium-sparing diuretics work by binding ENaCs (amiloride, triamterene) or blocking aldosterone receptors to reduce sodium reabsorption in the collecting tubule (spironolactone, eplerenone). This reduces water retention and avoids excessive K+ excretion in the urine, preventing hypokalemia Mechanism of action:

Sodium is normally reabsorbed in a renal nephron's collecting tubules. This is accomplished through epithelial sodium channels, also known as ENaCs, which are found on the luminal surface of the main cells that border the collecting tubules. When positively charged Na+ enters the cells during reabsorption, it creates an electronegative luminal environment, causing potassium (K+) to be produced into the lumen/ urine in exchange.[15] Water retention is also caused by sodium reabsorption.

The renin–angiotensin–aldosterone system (RAAS) is triggered when the kidneys detect low blood pressure, and aldosterone is eventually produced.

Potassium-sparing diuretics work by binding ENaCs (amiloride, triamterene) or blocking aldosterone receptors to reduce sodium reabsorption in the collecting tubule (spironolactone, eplerenone). This reduces water retention and avoids excessive K+ excretion in the urine, preventing hypokalemia.[16]

These diuretics are not utilised as main therapy for hypertension since they are weakly natriuretic and do not generate clinically significant blood pressure decreases.[8] They can be combined with other antihypertensives or medications that cause hypokalemia to help keep potassium levels in the normal range. For example, they are often used as an adjunct to loop

diuretics (usually furosemide) to treat fluid retention in congestive heart failure and ascites in cirrhosis.[17] Shown in fig 6.

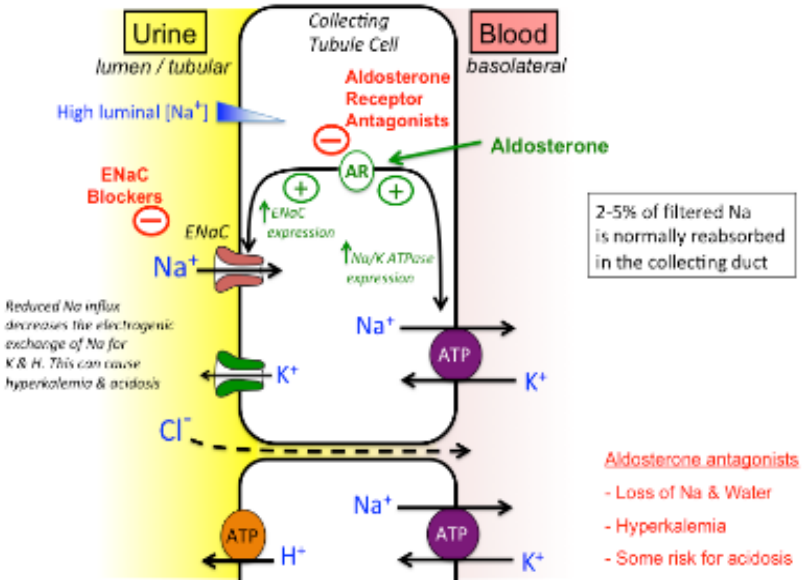
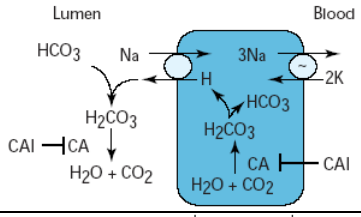
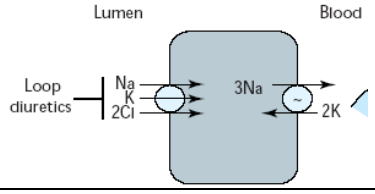
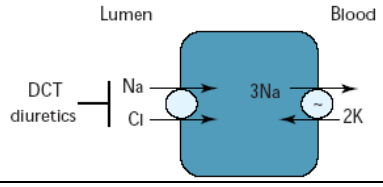
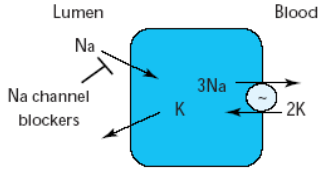


Fig. 6: Mechanism of potassium sparing diuretic.

Diuretic (color coded)	Site of Action	Mechanism of Action	Side Effects
Osmotic Diuretic (e.g. Mannitol)	Proximal Convoluted Tubule	Non-metabolizable osmotic diuretic filtered into the tubular space where it increases tubular fluid osmolality	Pulmonary edema Hypo or hypernatremia
Carbonic Anhydrase Inhibitors (Acetazolamide)	Proximal Tubule	Impedes $HCO3^-$, H^+, Na^+ reabsorption by inhibition of CA 	$HCO3^-$ loss Acidosis Skin toxicity Sulfa drug related allergies
Loop Diuretics (e.g. Furosemide)	Thick Ascending Limb (Ascending loop of Henle)	Blocks Cl^-, Na^+ and K^+ reabsorption (via Na^+/K^+ $2Cl^-$ pump) 	$\downarrow Na^+$ $\downarrow K^+$ $\downarrow Mg^{2+}$ Metabolic alkalosis Ototoxicity Hypocalcemia
Thiazides	Thick Ascending Limb And Early Distal Tubule	Inhibit Na^+ and Cl^- transport (via Na^+/Cl^- symport)	$\downarrow Na^+$ Cl^- $\downarrow K^+$ Metabolic alkalosis

			Hypercalcemia Hyperuricemia Photosensitivity
Aldosterone Antagonists (K^+ sparing)	Late Distal Tubule and Collecting Duct	Blocks aldosterone-stimulated Na^+ reabsorption and K^+ and H^+ excretion in late distal tubule and collecting duct	Hyperkalemia Hirsuitism, Gynecomastia
Renal Epithelial Na Channel Inhibitors (K+ sparing, e.g. Amiloride)	Late Distal Tubule and Collecting Duct	Inhibit Na+ reabsorption which inhibits K+ and H+ transport into urine since driven by Na+ gradient 	Hyperkalemia

CONCLUSION

Diuretics are a broad class of medications that are still crucial in the treatment of hypertension and hypervolemia. Diuretics such as loop diuretics, thiazides, and potassium chloride Sparing agents, such as osmotic diuretics, are effective in the treatment of hypertension while having little adverse effects. In selective ion reabsorption, their effect is dependent on the site of action on the Nephron.

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