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Clinical use of Loop Diuretics Acting on Symporters

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ABSTRACT

Loop diuretics, targeting the Na-K-2Cl symporter (NKCC2) in the thick ascending limb of the loop of Henle, are pivotal in managing fluid overload and electrolyte imbalances. By inhibiting NKCC2, these drugs reduce sodium, chloride, and potassium reabsorption, diminishing interstitial osmolarity and enhancing water excretion. This mechanism underpins their efficacy in treating congestive heart failure, liver cirrhosis, renal failure, and resistant hypertension, offering rapid symptom relief despite no proven survival benefit. Additionally, loop diuretics are utilized off-label for emergent hyperkalemia and hypercalcemia due to their kaliuretic and calciuretic effects. Four loop diuretics—furosemide, bumetanide, torsemide, and ethacrynic acid—vary in potency, bioavailability, and metabolism. Bumetanide is the most potent, while torsemide's longer half-life and hepatic metabolism favor specific patient profiles. Intravenous administration achieves faster diuresis but necessitates close monitoring to avoid complications like hypotension and acute kidney injury. Adverse effects include electrolyte disturbances (hypokalemia, hypomagnesemia, hypocalcemia), ototoxicity (especially with ethacrynic acid), and metabolic derangements (hyperuricemia, hyperglycemia). Guidelines from the AHA and ACC recommend loop diuretics as first-line therapy for heart failure with fluid overload and in hypertension with renal impairment. However, their use requires careful electrolyte monitoring and dose adjustments based on renal/hepatic function. Despite comparable mortality outcomes among agents, torsemide may offer advantages in reducing hospitalizations. Clinicians must balance efficacy against risks, emphasizing personalized therapy to mitigate adverse effects while addressing the underlying pathophysiology. Loop diuretics remain indispensable in clinical practice, underscoring the need for judicious application to optimize patient outcomes.

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Introduction

Loop diuretics are a class of medications acting on the loop of Henle located in the juxtamedullary nephron between the renal cortex and medulla to increase urine production via eliminating bodily salt and water. Albeit not proven to improve overall survival, loop diuretic has been approved by the Food and Drug Administration (FDA) for more than half a century upon treating fluid overload secondary to diverse pathologies including congestive heart failure, liver cirrhosis, and renal failure to relieve symptoms and signs such as shortness of breath, pleural effusion, ascites, and peripheral edema. Furosemide, the first approved loop diuretic, is the fifteenth most commonly prescribed drug in the United States owing to its prompt and significant effectiveness in reducing morbidity as well as the broad spectrum of diseases it covers [1,2].

The pronounced efficacy of loop diuretic is rooted from the blockage of Na-K-2Cl cotransporter a symporter located at the apical membrane of the tubular cells at the thick ascending limb of the loop of Henle, as a competitive chloride (Cl-) antagonist so sodium and chloride cannot be reabsorbed from the filtrate in the tubular lumen to tubular cells, and then to interstitium [3,4]. Whereupon, the interstitial osmolarity and tonicity, largely reflected by the interstitial sodium and chloride concentration, would decrease. Water then moves from interstitium to the nearby descending limb of the loop of Henle, driven by the osmolar gradient between the lumen and interstitium. This consequently augments urine output and lessens tissue edema. Blood pressure would also decrease as the blood volume is now reduced, so loop diuretic is also approved by the FDA to treat hypertension. It is more efficacious in resistant hypertension when the patient is refractory to at least three other classes of antihypertensives [5].

Na-K-2Cl symporter inhibition also prevents potassium reabsorption from the filtrate to cause an increase in urinary potassium loss and disrupts the transmembrane potential gradient that is essential for calcium and magnesium reabsorption back to interstitium and blood, so clinicians frequently resort to loop diuretics when encountering life-threatening hyperkalemia to emergently lower serum potassium level or to use it off-label for hypercalcemia and hypermagnesemia [6,7].

Na–K–2Cl Symporter And Its Physiological Role

Nephron is the basic structural and functional unit of the kidney. There are two types of nephrons: cortical and juxtamedullary [8]. The horseshoe-shaped loop of Henle predominantly exists in the juxtamedullary nephron. Loop of Henle consists of the descending limb and the ascending limb. Although the descending limb is thin, the ascending limb has both thin and thick segments (Figure 1). The descending limb, connected proximally to the proximal convoluted tubule, dips deeply into the medulla before turning upward to form the ascending limb, which subsequently evolves into the distal convoluted tubule.

The descending limb is lined up by squamous cells to allow water permeability whereas the ascending limb, made of tubular cells

of histologically columnar epithelium is waterproof [9,10]. Four membrane proteins in the tubular cell of the ascending limb take part in the transportation of electrolytes between the tubular lumen and interstitium: Na,K-ATPase, Na–K–2Cl symporter, ROMK K+ channel, and ClC–Kb Cl− channel.

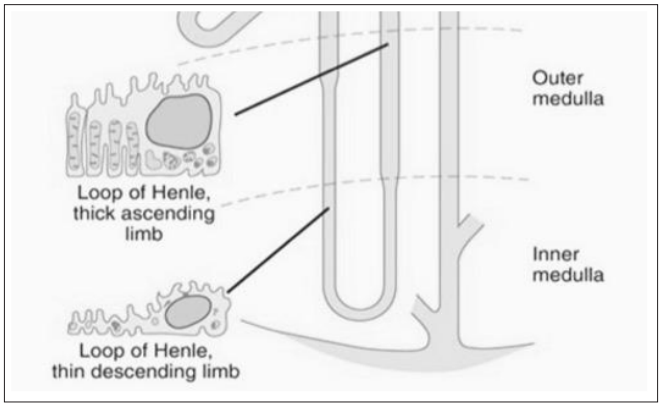

Figure 1: Loop of Henle. The Thick Ascending Limb is Surrounded by Columnar Renal Tubular Cells. The Thin Descending Limb is Surrounded by the Flat Squamous Cells

Na,K-ATPase is at the basolateral membrane of the tubular cell which constantly pumps sodium (Na+) out of the cell to interstitium, against its concentration gradient, while potassium (K+) is moved concurrently in the opposite direction also via the Na,K-ATPase [11]. The osmolarity of interstitium therefore is elevated due to higher sodium concentration, can be as high as 1200 mOsm/kg at the tips of the papillae, which propels the movement of water from the isotonic filtrate across the wall of the descending limb to the hypertonic interstitium a process called water osmosis [12]. Na–K–2Cl symporter, on the other hand, is at the apical membrane of the tubular cell, which has 12 transmembrane domains with intracellular amino and carboxyl terminals.

As the intracellular sodium concentration is reduced due to Na,K-ATPase actively pumping sodium outwardly, a secondary active transport by Na–K–2Cl symporter is triggered to simultaneously move one Na+, one K+, and two Cl− from the lumen to the tubular cell [13]. The concomitant increase in intracellular potassium concentration through Na–K–2Cl symporter facilitates K+ diffusion back to lumen and to interstitium mainly via ROMK channel that is found in both apical and basolateral membrane of the tubular cell [14]. In parallel, the elevated intracellular chloride concentration would drive Cl- moving from cell to interstitium via ClC–Kb channel existing in the basolateral membrane of the tubular cell (Figure 2) [15].

As a result, there is a net movement of sodium, chloride, and potassium from the filtrate in the lumen of the ascending limb, across the tubular cell, to interstitium. In the meantime, water is diffused through osmosis from the lumen of descending limb to interstitium owing to the high interstitial osmolarity generated by the net influx of sodium and chloride by the conjoint effort of Na,K-ATPase and Na–K–2Cl symporter [16]. The movement of sodium leading to the movement of water in the loop of Henle is called countercurrent multiplication [17].

50%–60% of filtered magnesium and 20% of filtered calcium in the filtrate are reabsorbed via the paracellular tight junctions between the tubular cells in the thick ascending limb segment driven by the transmembrane potential difference that is accumulated when potassium diffuses through the ROMK K+ channel at the apical membrane back to lumen to create a relatively positive intraluminal electricity [18].

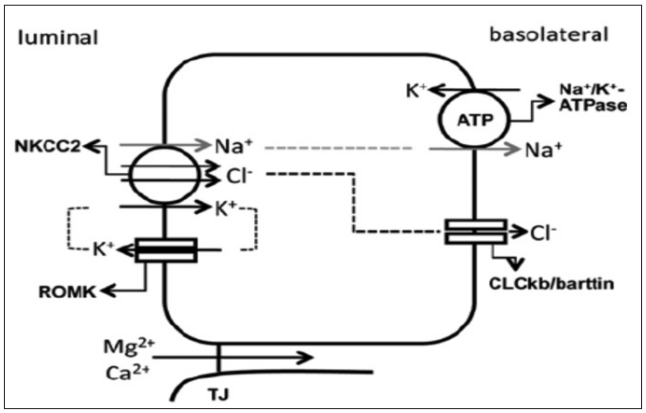

Figure 2: A Renal Tubular Cell at the Ascending Limb. Na+ is Transported out of the cell to interstitium by Na,K-ATPase in the basolateral membrane. The Na–K–2Cl symporter, named NKCC2 here, transports Na+, Cl-, and K+ into the tubular cell by secondary active transport. Cl− exits through basolateral ClC–Kb Cl− channels. K+ moves from the cell to interstitium and lumen by ROMK K+ channels. TJ, the tight junction where Mg2+ and Ca2+ are transported from lumen to interstitium [19].

Inhibition of Na–K–2Cl Symporter by Loop Diuretic and the Impacts

Loop diuretic blocks the Na–K–2Cl symporter so sodium, potassium, and chloride ions cannot be absorbed from the lumen to interstitium. The osmolarity and tonicity of interstitium hence decreases and less water is diffused from lumen to interstitium at the descending limb. The more water that stays as filtrate eventually is excreted as urine, along with an increase in sodium, chloride, and potassium in the urine.

Since Na–K–2Cl symporter undertakes 25% of the overall sodium reabsorption and 15% of the water resorption in kidney Na–K–2Cl symporter impediment would cause remarkable sodium and water excretion [20]. Loop diuretic therefore is highly potent compared to other diuretics such as thiazide and potassium-sparing diuretic that each only inhibits the reabsorption of 5% of luminal sodium in the distal convoluted tubule and in the collecting duct respectively (Figure 3) [21].

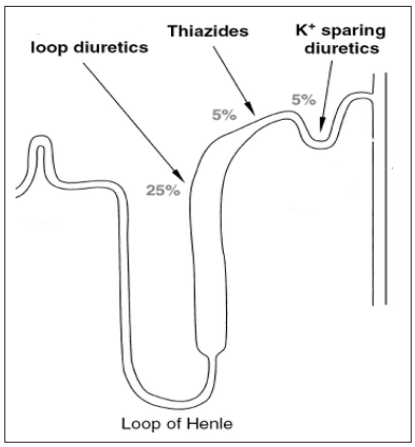

Figure 3: A partial nephron showing sites of action of diuretics along the various segments. Loop diuretic is the most potent diuretic as it inhibits 25% of the sodium reabsorption versus 5% for thiazide at the distal convoluted tubule and 5% for potassium

sparing diuretic in collecting duct [22].

Similarly, Na–K–2Cl symporter blockage suppresses potassium reabsorption from lumen to interstitium, giving rise to an increase in urinary potassium loss to cause bodily potassium depletion. Besides, increased sodium delivery to the distal convoluted tubule where the Na-K exchanger is located facilitates potassium efflux into urine in exchange of sodium influx from lumen. Both contribute to hypokalemia.

Notwithstanding, a fraction of potassium would diffuse back to lumen through ROMK K+ channel to be excreted as urine due to elevated potassium concentration in the tubular cell, when the Na–K–2Cl symporter is functional. This potassium efflux would no longer be present considerably when the symporter is blocked, which in turn fails to generate sufficient transmembrane potential to prompt calcium and magnesium reabsorption in the ascending limb so both metal ions are more significantly lost in urine as hypercalciuria and hypermagnesuria, causing hypocalcemia and hypomagnesemia [23].

Indications and Clinical Usage of Loop Diuretic

Class I recommendation is given to loop diuretic per American Heart Association (AHA) guidelines as the first line treatment of heart failure with reduced left ventricular (LV) ejection fraction and fluid overload to alleviate pulmonary congestion/edema and peripheral edema [24]. Patients hospitalized with heart failure due to symptoms/signs of fluid overload should be treated with intravenous (IV) loop diuretic for morbidity relief [25].

Grade A recommendation advocates using loop diuretic to treat ascites due to liver cirrhosis [26] refractory to spironolactone, which nonetheless mandates in-hospital monitoring as the fluid and electrolyte alliteration may precipitate hepatic coma [26,27]. The edema due to chronic kidney disease including the nephrotic syndrome can often be mitigated by loop diuretic empirically [28].

Grade B recommendation from the Eighth Joint National Committee suggests using loop diuretic to treat hypertension as a second line due to its lower efficacy as to other antihypertensive classes and the lack of data to support improvement in cardiovascular outcomes [29]. However, class I recommendation per American College of Cardiology/AHA Task Force proposes to prescribe loop diuretic for hypertension in adults of heart failure with symptoms/signs of fluid overload and preserved LV ejection fraction, with a glomerular filtration rate < 30 mL/min, or with resistant hypertension [30].

Loop diuretic can also be used off-label for life-threatening hyperkalemia as it increases potassium elimination in urine, yet the onset of action is slow (at least one hour) and the effect is inconsistent and unpredictable [31]. As loop diuretic also removes calcium and magnesium from the body, it is empirically used in treating hypercalcemia and hypermagnesemia as well [32,33].

Pharmacokinetics of Loop Diuretic

Four loop diuretics are available in the United States: furosemide, bumetanide, and torsemide, and ethacrynic acid (Table 1) in both oral and IV forms. Ethacrynic acid is derived from phenoxyacetic acid whereas the others are sulfa-based [34]. IV is more potent than oral form, is reserved for rescue purposes, and is administered mainly to hospitalized patients as close monitoring of hemodynamics and electrolytes is mandated for overdiuresis [35]. Bumetanide has the highest potency among all, followed by torsemide, then furosemide and ethacrynic acid [4].

The onset of action is 30-60 minutes for oral form and 5-10 minutes for IV form, whereas the duration of action, correlating with each's half-life, differs among the four [4]. Torsemide has the longest half-life, followed by furosemide, then ethacrynic acid, and bumetanide the shortest. The oral bioavailability also varies. Ethacrynic acid is close to 100%, followed by torsemide and bumetanide at 80%, and furosemide the lowest at 60% [4].

Torsemide is mainly metabolized via liver (80%) than excreted unchanged urinarily [36]. For the other three, more than 60% of loop diuretic is excreted in the urine unchanged, with the remainder either metabolized through kidney (furosemide and ethacrynic acid) or liver (bumetanide). Therefore, the duration of action is prolonged for furosemide and ethacrynic acid in patients with renal diseases, whereas it is prolonged for torsemide and bumetanide in patients with liver diseases. Dosage adjustment may be required based on their underlying diseases.

Table 1: Inhibitors of Na-K-2Cl Symport. M, metabolism; R, renal excretion of intact drug. *M, Metabolism of furosemide occurring predominantly in kidneys

Drug	Relative Potency	Oral Availabiltiy	Half-life (hours)	Elimination
Furosemide	1	60%	1.5	65%R, 35%M*
Bumetanide	40	80%	0.8	62%R, 38%M
Ethcrynic acid	0.7	100%	1	67%R, 33%M
Torsemide	3	80%	3.5	20%R, 80%M

Torsemide improves functional status, decreases hospitalizations, and lowers cardiac mortality in patients with heart failure than furosemide but the overall mortality is similar at 12 months after hospital discharge [37,38]. Another trial confirmed that in patients with heart failure, overall mortality is of no notable difference between bumetanide, furosemide, and torsemide [39]. Therefore, the choice of loop diuretic should be based on side effect profiles.

Adverse Effects of Loop Diuretic

Overdiuresis leads to volume depletion, dehydration, hypotension and acute kidney injury secondary to reduction in renal perfusion [40]. An increase in serum creatinine as a result of poor renal perfusion is also common [41].

Hypokalemia, hypocalcemia, and hypomagnesemia can be potentiated and all three cause fatal arrhythmia. Prolonged hypocalcemia from hypercalciuria can aggravate osteoporosis [42]. Likewise, hyponatremia and hypochloremia occur with loop diuretics. Hypochloremia causes metabolic alkalosis by increasing the reabsorption of bicarbonate in the distal tubule to maintain extracellular electrical neutrality [43].

Ototoxicity ranging from ear fullness to irreversible hearing loss [42] has been reported and the risk factors include IV administration, higher dosage, and ethacrynic acid [44,45]. Meanwhile, sulfonamide-based loop diuretics may cause idiosyncratic hypersensitivity reactions [46].

Loop diuretics may bring about hyperuricemia, hyperglycemia, and hyperlipidemia. Prolonged hyperuricemia and hyperglycemia lead to gout and diabetes mellitus respectively [47,48]. Hyperlipidemia varies from increase in plasma triglycerides and low-density lipoprotein cholesterol to decrease in plasma high-density lipoprotein cholesterol [4].

Conclusion

Several inferences can be drawn on loop diuretic, based upon the aforementioned discussion:

- Loop diuretic is a potent diuretic, for the Na-K-2Cl symporter it inhibits shoulders more sodium reabsorption among all the available diuretics. It can be used for urgent symptomatic relief (e.g., pulmonary edema from congestive heart failure) or in refractory circumstances (e.g., resistant hypertension).
- Loop diuretic is indicated in a wide array of conditions including fluid overload secondary to congestive heart failure, liver cirrhosis, and renal failure, as well as hypertension and life-threatening hyperkalemia, making it frequent prescription.
- The pharmacodynamics differs among the available loop diuretics and clinicians shall choose the one that caters to the individual patient profile.
- A variety of adverse effects can emerge for Na-K-2Cl symporter blockage affects transportation of various electrolytes, so clinicians need to cautiously monitor for hemodynamic status, metabolic adversity, and electrolyte imbalance [49,50].

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