INVITED ARTICLE

# Diuretics in Acute Kidney Injury

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Acute kidney injury (AKI) is a fairly common complication encountered in the intensive care unit (ICU). The development of AKI, and especially the need for renal replacement therapy (RRT), increases the risk of mortality.[1]

Patients suffering from AKI are often prescribed diuretics by their treating physicians, and loop diuretics are the class of diuretics that are most frequently prescribed in this situation.

This review will therefore focus mainly on the role of loop diuretics in AKI.

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## Pharmacology of Loop Diuretics

Loop diuretics are weak organic acids that inhibit the sodium/potassium chloride cotransporter, which is present in the tubular epithelial cells in the thick ascending loop of Henle.[2] Usually around 30–40% of the filtered load of sodium is reabsorbed in this portion of the nephron. By inhibiting this cotransporter, loop diuretics reduce the oxygen consumption of the tubular cells and in theory might protect these cells from ischemia.

Furosemide causes greater loss of water than sodium loss, resulting in the production of hypotonic urine. Loop diuretics also cause increased urinary excretion of potassium, calcium, and magnesium by inhibiting the passive reabsorption of these ions. Other organic acids (cephalosporin, ciprofloxacin, oseltamivir, etc.) might compete with loop diuretics and reduce their action.[3]

Over 95% of the loop diuretics are bound to albumin. Therefore, they do not undergo glomerular filtration. They reach their target site by active secretion from the blood into the urine by the organic acid transporters present in the proximal tubules. Hypoalbuminemia (which is common in patients with AKI in the ICU) leads to a decreased secretion into the tubules and an increased clearance of loop diuretics. The diuretic effect of loop diuretics is therefore considerably reduced in the presence of hypoalbuminemia.[4] Other highly protein-bound drugs such as phenytoin or warfarin may also decrease the action of loop diuretics. There is a theoretical rationale, therefore, for combining loop diuretics with an albumin infusion. A meta-analysis of 10 studies has concluded that in hypoalbuminemic patients, fluid balance is better achieved when furosemide and albumin are administered together. In patients with normal albumin levels, this combination probably has no benefit.[5]

Delivery of loop diuretics into the tubules is also decreased when there is renal dysfunction. A reduced renal blood flow which is not uncommon in patients with AKI further compounds this decreased secretion.[6] Metabolic acidosis further decreases the tubular secretion of loop diuretics.

This means that in patients with AKI, the dose of diuretics needed to achieve diuresis may be much higher than usual.[7] It is also commonly believed that a continuous infusion of a loop diuretic might be more effective than intermittent boluses. Several studies have demonstrated that while it is easier to achieve a steady diuresis with continuous furosemide infusion, there is no effect on renal function or electrolyte disturbances or mortality.[8]

It is also important to understand that there is a threshold dose of loop diuretics below which they will not have any action. There is also a ceiling dose above which there is no additional benefit.[9] Once this dose is reached, a diuretic acting on another location of the nephron, e.g., thiazide diuretics may be added for added effect. Electrolyte levels (especially potassium) should be monitored regularly when this combination of diuretics is being used.[10]

The clearance of furosemide is delayed in patients with AKI; however, torsemide and bumetanide are metabolized in the liver and their half-lives are not prolonged in AKI.[3]

Potential benefits of loop diuretics in AKI:

- Loop diuretics might decrease the oxygen consumption of the thick ascending limb of Henle by interfering with its function and thus protect it from ischemia.
- Loop diuretics inhibit prostaglandin dehydrogenase, as a result of which there is a decreased breakdown of prostaglandin $E_2$ which is a renal vasodilator. Loop diuretics might therefore increase the renal blood flow.[11]
- Maintaining urine flow might prevent tubular obstruction and resultant backflow of glomerular filtrate by flushing out any debris blocking the tubules.[12]
- Some studies have concluded that oliguric AKI has a worse prognosis than nonoliguric AKI. Loop diuretics are therefore prescribed to convert an oliguric AKI into a nonoliguric AKI.
- Patients in the ICU with AKI and oliguria often receive lots of fluids as carriers for antibiotics, vasopressors, and nutrition and are in danger of developing fluid overload. Diuretics simplify fluid management of such patients.

Potential harm caused by loop diuretics:[6]

- Loop diuretics decrease the effective circulating volume through venodilation or diuresis and may cause a decrease in renal blood flow (through renin) and glomerular filtration rate.

- Although it is commonly believed that loop diuretics clear tubular obstruction, some studies suggest that loop diuretics acidify the urine and thereby actually increase the aggregation of Tamm-Horsfall protein in the tubules, thus worsening tubular blockage.
- Loop diuretics may cause electrolyte abnormalities and metabolic alkalosis. A significant risk of ototoxicity is observed if high doses of loop diuretics are administered to patients with AKI. There is also some evidence that they impair mucociliary clearance in the respiratory tract and may have some immune-suppressive effects.

Although diuretics are used commonly in AKI, there is no clear evidence that they improve outcomes in AKI.

According to Mehta et al.,[13] who studied 552 patients with acute renal failure, diuretic use was associated with an increased in-hospital mortality and nonrecovery of renal function. Patients who did not respond to diuretics had worse outcomes than patients who responded to diuretics or those who did not receive diuretics.

In another randomized controlled trial of 92 patients,[14] loop diuretics did increase urine output but did not affect the recovery of renal function, did not decrease the need for dialysis, and did not decrease mortality at 21 days. Like in the previous study, patients who remained oliguric had the worst outcomes.

In a meta-analysis by Bagshaw et al.,[15] 62 studies were reviewed. They concluded that loop diuretics had no effect on mortality. However, loop diuretics increased urine output and decreased the duration of continuous RRT. Creatinine levels declined faster in patients treated with loop diuretics.

The recent SPARK study[16] which studied the effect of low-dose furosemide in critically ill patients with AKI concluded that furosemide did not prevent worsening AKI, did not reduce RRT use, nor did it improve kidney recovery. Moreover its use was associated with more minor electrolyte abnormalities.

Therefore, while the urine output might increase with diuretics. Evidence that loop diuretics decreases mortality, reduces the need for dialysis, or limits the length of ICU stay is lacking. While caring for patients with AKI, the focus should be on identifying any reversible causes of renal damage, stopping any potential nephrotoxic agents, optimizing hemodynamics, and correcting electrolyte abnormalities.[12,17]

However, critically ill patients often receive large volumes of fluids. Loop diuretics in such patients minimize fluid overload and may make patient management easier. On the basis of the current evidence, therefore, the use of diuretics should be limited to the management of volume overload and/or hyperkalemia. Patients should undergo dialysis promptly when indicated and the use of diuretics should not delay the institution of dialysis.

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