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Are Diuretics Harmful in the Management of Acute Kidney Injury?

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Abstract and Introduction

Abstract

Purpose of review To assess the role of diuretics in acute kidney injury (AKI) and their effectiveness in preventing AKI, achieving fluid balance, and decreasing progression to chronic kidney disease (CKD).

Recent findings Diuretics are associated with increased risk for AKI. The theoretical advantage of diuretic-induced preservation of renal medullary oxygenation to prevent AKI has not been proven. A higher cumulative diuretic dose during the dialysis period can cause hypotension and increase mortality in a dose-dependent manner. Data on the use of forced euvolemic diuresis to prevent AKI remains controversial. Positive fluid balance has emerged as an independent predictor of adverse outcomes. Post-AKI furosemide dose had a favorable effect on mortality due in part to the reduction of positive fluid balance. There are exciting experimental data suggesting that spironolactone may prevent AKI once an ischemic insult has occurred and thus prevent the progression to CKD.

Summary Diuretics are ineffective and even detrimental in the prevention and treatment of AKI, and neither shorten the duration of AKI, nor reduce the need for renal replacement therapy. Diuretics have an important role in volume management in AKI, but they are not recommended for the prevention of AKI. There is increased emphasis on the prevention of progression of AKI to CKD.

Introduction

The fortuitous discovery of organic mercurial compounds with diuretic properties (merbaphen) by Arnold Vogl[1,2] heralded the era of diuretic therapy in clinical practice. Since then, the search for less toxic synthetic compounds resulted in the introduction of carbonic anhydrase inhibitors (CAIs) in the 1950s, thiazides, loop diuretics, potassium-retaining diuretics and ion-transport modulators in the 1960s and 1970s, and, more recently, the discovery of small-molecule inhibitors of urea transport.[3] The different classes of diuretics, by virtue of their unique chemical and pharmacologic characteristics, have different effects on anatomically and functionally distinct segments of the nephron. Loop diuretics act on the thick ascending loop, thiazides on the early distal tubule, and the potassium-sparing diuretics act on the distal tubule and cortical collecting ducts. The duration of action can vary from 4–6 h with a loop diuretic such as furosemide, to 50–60 h with a thiazide diuretic such as chlorthalidone. In addition to diuresis, polyvalent diuretics can lower elevated blood pressure and cause metabolic effects such as uricosuria, hypertriglyceridemia, and hyperglycemia.

Loop diuretics, such as furosemide and bumetanide, are commonly used in clinical practice. Loop diuretics exert their natriuretic effect after secretion into the proximal collecting duct via organic anion transporters and then inhibiting NKCC2 transport in the thick ascending loop of Henle. Bumetanide has an in-vitro transport inhibitory potency and an in-vivo natriuretic effectiveness, that is approximately 50-fold that of furosemide, with a consequent potential for increased effectiveness and decreased incidence of adverse effects.[4] Thiazides, CAIs, aquaretics (vaptans), and osmotic agents are rarely used to manage acute kidney injury (AKI) and are not discussed further here. Of interest, however, is the emerging role of 'nontraditional diuretic' compounds with natriuretic and diuretic properties in the treatment of AKI. Among them, natriuretic peptides have attracted much attention because of their ability to cause renal vasodilation, natriuresis, and preservation of glomerular filtration rate (GFR) without affecting the renal blood flow.[5]

Pathophysiologic Considerations in the Management of Acute Kidney Injury

AKI is a complex disorder caused by a range of factors, occurring in various clinical settings and manifesting as anything from a mild increase in serum creatinine (SCreat) to anuria with resultant uremic signs and symptoms. AKI is defined in this article as an absolute increase in SCreat of at least 0.3 mg/dl from baseline or a percentage increase in SCreat of at least 50% from baseline within 48 h, or a reduction in urine output, defined as less than 0.5 ml/kg/h for more than 6 h.[6] Impaired renal blood flow autoregulation related to vasoconstriction may have a role in the pathogenesis of AKI.[7] A significant decrease in renal blood flow can cause hypoxic injury to the renal tubular cells by depleting intracellular ATP, disrupting intracellular calcium homeostasis, generating free radicals, activating inflammatory pathways, and causing cellular changes that destroy the integrity of the cytoskeletal structure.[8,9] The damaged renal tubular cells form casts that obstruct the tubular lumen and cause backleak of filtrate. Management of AKI is directed at multiple trigger points in the complex pathomechanistic cascade of AKI – from prevention to alleviation of symptoms.

Animal studies have suggested that diuretics, particularly loop diuretics, might decrease the tubular reabsorption and metabolic demand. However, an increase in distal tubule sodium delivery can increase the metabolic cost of sodium reabsorption[10] and activate the renin–angiotensin–aldosterone system (RAAS) and sympathetic nervous system, resulting in adverse outcomes.[11] Randomized clinical trials in humans have shown contradictory results, with some showing modest clinical benefit, and others no effect or a detrimental effect. In this article, we review the pathophysiological basis of the use of diuretics in AKI, followed by a critical examination of the current evidence supporting or refuting the effectiveness of the clinical application of diuretics.

Diuretics in the Management of Acute Kidney Injury

Diuretics are often used to increase the urine output to prevent AKI, achieve fluid balance, hasten renal recovery, and to decrease the progression of AKI to chronic kidney disease (CKD). Their performance in this regard is discussed.

Prevention of Acute Kidney Injury

The effectiveness of diuretics in the management of AKI is controversial, an issue complicated by the nonuniformity of clinical settings, timing of intervention, and differing endpoints used in clinical studies. Experimental evidence exists suggesting that alterations in microcirculation in the renal cortex or renal medulla can occur despite normal or increased global renal blood flow leading to AKI through the interlinked occurrence of renal hypoxia and activation of inflammatory pathways. Regional, intrarenal hypoxia can also trigger renal adaptive responses that downregulate oxygen consumption for tubular transport and preserve cellular integrity.[12,13] It is postulated that decreasing the GFR and tubular workload (because of decreased medullary sodium reabsorption) in AKI can contribute to an improved oxygen supply/demand relationship by reducing oxygen consumption and increasing medullary oxygenation, and thus protecting the nephron from further ischemic injury.[14] Under experimental conditions, loop diuretics have been reported to protect the chronically hypoxic juxtamedullary regions during oxidative stress by decreasing the GFR and tubular workload.[14–16]

However, human studies looking at the changes in renal hemodynamics in response to furosemide have shown conflicting results. In a clinical study, an infusion of furosemide in patients with normal renal function undergoing cardiac surgery was associated with increases in urine flow and fractional excretion of sodium and decreases in GFR, filtration fraction, tubular sodium reabsorption, and renal oxygen consumption, suggesting the potential to improve the oxygen supply/demand relationship in AKI.[17] However, in a subsequent study, the continuous infusion of furosemide 2–6 days after cardiac surgery increased renovascular resistance and decreased GFR, but caused an unexpected increase in the renal oxygen consumption in patients with AKI.[18] The role of furosemide in the prevention and treatment of AKI was further investigated in several prospective, randomized clinical trials (PRCTs). In patients with normal renal function (n = 126), the continuous infusion of furosemide for 48 h, starting in the preoperative period, was associated with higher postoperative SCreat levels and incidence

of AKI compared with the control group.[19] This finding that furosemide was ineffective, without significant clinical benefits, and even detrimental in the prevention and treatment of AKI was further corroborated by a meta-analysis of 9 PRCTs involving 849 patients.[20]

Preoperative use of diuretics increased the risk for AKI [odds ratio (OR) 1.68, 95% confidence interval (CI) 1.41–2.00] in the recently reported FINNAKI (AKI in adult ICU patients in Finland) study.[21] Smaller studies have tried to find high-risk subgroups or secondary outcomes that benefit from furosemide. In a Brazilian study, diuretic use in the ICU setting, especially in older patients with low mean arterial pressures and PaO_2/FiO_2, was associated with a three-fold to five-fold increased risk of AKI.[22] In established AKI, diuretics neither shorten the duration of AKI, nor reduce the need for renal replacement therapy (RRT),[23] but can be associated with a significant increase in the risk of death or nonrecovery of renal function, particularly in critically ill patients.[24] Of interest is the finding that diuretic usage at the initiation of dialysis in the postoperative period did not affect renal recovery, but that a higher cumulative diuretic dose during the dialysis period was associated with hypotension and higher mortality in a dose-dependent manner.[25] Attempts at the conversion of oliguria to nonoliguric AKI in the setting of severe, underlying renal vasoconstriction may therefore be counterproductive.

Does forced diuresis with the theoretical advantage of volume expansion, RAAS suppression, inhibition of renal vasoconstriction, and tubular obstruction have a role in the prevention of AKI in high-risk patients? Most of the studies involving forced diuresis have been in intoxication, such as with salicylates or tubular toxins such as contrast or pigment nephropathy. Forced euvolemic diuresis with saline, mannitol, and furosemide in a Canadian cohort was associated with positive fluid balance and higher risk of contrast-induced nephropathy.[26] A different conclusion was reached in the MYTHOS (Induced Diuresis with Matched Hydration Compared to Standard Hydration for Contrast Induced Nephropathy Prevention) trial. The investigators reported in this unblinded study that furosemide-forced diuresis and intravenous saline hydration (rate of ~600 ml/h for up to 6 h), matched with urine output using a dedicated device, reduced the incidence of AKI compared to controls in CKD patients undergoing cardiac procedure with contrast agents.[27] Despite the favorable results reported in the latter study, caution is advised in the adoption of forced diuresis to prevent AKI until more conclusive data is available. Mannitol has been recommended in rhabdomyolysis because of its ability to decrease tubular toxicity by increasing urinary flow, acting as a free radical scavenger, and decreasing the possibility of compartment syndrome.[28] The use of a loop diuretic in combination with bicarbonate therapy has been recommended on the basis of retrospective uncontrolled trials. In the absence of PRCTs, we do not recommend the routine use of diuretics and suggest that they should be limited to patients who are volume replete or expanded.

Achieve Fluid Balance

Positive fluid balance is a common finding in critically ill patients, associated with increased capillary permeability in specific microcirculation beds, interstitial and cellular edema, disruption of cellular energy and transport functions, and progression to organ damage. Positive fluid balance is an independent predictor of AKI[29,30,31] and mortality.[32,33] In the PICARD (Program to Improve Care in Acute Renal Disease) study, a 10% increase in body weight relative to baseline during ICU stay was associated with higher 60-day mortality and nonrecovery of renal function.[32] Predictably, volume management is an integral part of the care of patients with AKI, and diuretics are often utilized with little clinical evidence. It is uncertain whether positive fluid balance is an epiphenomenon or causal in AKI. Although most studies have investigated the effect of positive fluid balance on adverse outcomes after the onset of AKI, a prospective observational study demonstrated that positive fluid balance occurred early in the intraoperative period during on-pump cardiac surgery and progressed into the postoperative period, and preceded the rise in SCreat.[30] One possibility for this observation may be related to early AKI because of the release of inflammatory mediators during surgery. However, the effect of protocol-driven fluid administration cannot be excluded. Indeed, fluid administration was not clearly associated with any identifiable volume-sensitive event. However, these findings require further investigation.

Data are emerging on the association between post-AKI fluid balance, diuretic use, and mortality. Secondary analysis of data from a multicenter, prospective cohort study in 10 Italian ICUs shows that nonsurviving AKI

patients had a higher positive mean fluid balance than surviving AKI patients, and that diuretic use was associated with better survival in this population (adjusted hazard ratio 0.25, 95% CI 0.12–0.52; $P < 0.001$).[31] Perhaps the best data to date come from the post-hoc analysis of data from FACTT (Fluid and Catheter Trial Therapy), a multicenter PRCT evaluating conservative vs. liberal fluid management strategy in patients with acute lung injury.[34] Fluid and diuretic management in the study were determined primarily by randomization and a specific algorithm based on hemodynamic measurements. A total of 306 patients from the original cohort who had developed AKI in the first 48 h of inclusion into the study were grouped into the conservative vs. liberal fluid strategy group for analysis. Fluid balance was defined as intake minus output from the onset of AKI to study day 7, death, or withdrawal from study. Critically ill acute lung injury patients in the conservative fluid group had less fluid accumulation and received more diuretics (furosemide: mean 73.5 mg/day). Positive fluid balance was associated with increased 60-day mortality (OR 1.61 per l/day, 95% CI 1.29–2.00, $P < 0.001$), whereas post-AKI furosemide dose was associated with decreased mortality (OR 0.54 per mean 100 mg/day, 95% CI 0.31–0.94). However, the protective effect of post-AKI was attenuated when adjusted for fluid balance (OR 0.61 per 100 mg/day, 95% CI 0.35–1.07, $P = 0.087$). The authors postulated that fluid balance is a causal intermediate in the interaction between diuretics and mortality, that is, the benefit of diuretics in this setting is because of reduction of fluid balance.

Diuretics may be useful in achieving fluid balance to facilitate mechanical ventilation, but hypovolemia, hyponatremia, and renal hypoperfusion can occur when excess fluids are removed in patients with AKI, as in decompensated heart and liver failure patients. Diuretic therapy is an independent predictor of AKI in heart failure patients,[35] 70% of AKI occurring within the first 48 h of diuretic treatment and associated with poor outcomes.[36,37] It is apparent from prior discussions that the efficacy of diuretics in achieving therapeutic fluid balance goals are dependent on the patient cohort studied, the setting, the timing, dose and duration of administration, and the underlying complexities of interaction of neurohormonal pathways. It is prudent to be aware that progressive severity of AKI is associated with increased severity of renal vasoconstriction, hypoxia, and downstream cascade of inflammatory events that impair vascular and parenchymal architectural integrity. Therefore, when the patient does not respond to diuretics, ever escalating use of these drugs will only lead to a delay in the initiation of RRT dialysis and increase the risk of unfavorable outcomes.

Decreasing the Progression of Acute Kidney Injury to Chronic Kidney Disease

Despite the lack of conclusive evidence, it is presumed that the association of AKI to progression of CKD represents a causal relationship.[38–41] In this scenario, the common pathway in the progression of AKI to CKD appears to be the initial impairment of oxygen balance causing renal tissue hypoxia and subsequent fibrosis.[42,43] Diuretics, by increasing medullary oxygenation, have been proposed as possible therapeutic candidates in the prevention of progression to CKD in such patients.[10,44] There are no long-term clinical studies addressing the hypothesis that preserving medullary oxygenation prevents progression of AKI to CKD. In fact, administration of furosemide following cardiac surgery caused an inappropriate increase in renal oxygen consumption.[18] In a study of 50 high-risk cardiac surgery patients, postoperative furosemide infusion did not decrease the incidence of 7-day AKI,[45] findings supported by numerous studies and summarized in a recent publication.[46]

Another interesting, but experimental approach to prevent the progression of AKI to CKD is the use of mineralocorticoid receptor blockers, a weak class of diuretics. Episodes of AKI can result in significant nephron loss and permanent alteration of renal capillary density, contributing to a urinary concentrating defect and the predisposition toward the development of renal fibrosis.[47] In animal models, spironolactone inhibited renal vasoconstriction,[48] prevented reduction in renal blood flow, decreased tubular apoptosis and the incidence of AKI. The protection conferred by spironolactone was characterized by decreasing oxidative stress and upregulation of endothelial nitric oxide synthase (eNOS) expression.[49,50] Recent experimental data show that ischemic AKI leads to the development of CKD with progressive increase in proteinuria, renal dysfunction, podocyte injury, glomerular hypertrophy, and focal sclerosis. Treatment with spironolactone either before or after ischemia prevented subsequent progression to CKD.[51] Although provocative, and despite abundant experimental evidence for its antifibrotic effect, clinical data supporting the use of mineralocorticoid receptor

blockers in AKI for the prevention of progression to CKD are unavailable. An important issue here may be the timing of the initiation and duration of mineralocorticoid receptor blockade after the onset of AKI, as RAAS blockade is a verified strategic option in many disease conditions, including CKD.[52] Although prevention therapies for AKI have not been satisfactory, current and evolving therapies have a greater potential for slowing the progression to CKD after an episode of AKI. Lessons from the CKD research will be invaluable.

Nontraditional Diuretics in Acute Kidney Injury

Among the many compounds with diuretic properties, natriuretic peptides deserve special mention. Natriuretic peptides cause selective dilatation of afferent arterioles and constriction of the efferent arterioles, resulting in increased GFR without affecting the renal blood flow.[5,17] Natriuretic peptides increase diuresis and natriuresis by blocking angiotensin-stimulated sodium and water absorption in the proximal tubules and amiloride-sensitive cation channels in the collecting ducts.[53] Despite these attractive properties, the effectiveness of natriuretic peptides in AKI has not been proven. In a PRCT, patients received a 5-day course of continuous nesiritide (B-type natriuretic peptide; at a dose of 0.01 µg/kg/min) or an identical appearing placebo, starting in the operating room immediately prior to surgery. Natriuretic peptides did not reduce the primary endpoint of incidence of dialysis and all-cause mortality through day 21, although they decreased the incidence of AKI.[54] The 5-day cumulative urine output and doses of diuretics were the same between the groups. Whether the observed renal benefits of nesiritide had any long-term impact on cumulative patient survival and renal outcomes was also investigated. The mean follow-up period of the 94 patients was 20.8 ± 10.4 months. No differences in cumulative survival between the nesiritide and control groups were noted (nesiritide 77.7 vs. placebo 81.6%, $P = 0.798$). The observed benefits of nesiritide to decrease the incidence of AKI may simply reflect a transient hemodynamic effect and the unfavorable long-term outcomes results may be explained by the findings of Swärd et al.[17] which showed that infusion of natriuretic peptides caused an increase in GFR and renal oxygen consumption without a proportional increase in renal blood flow, indicating a renal oxygen supply/demand mismatch and downstream effects of oxidative stress. These observations have several similarities with the clinical observations of diuretics in AKI and highlight the fact that diuretic-induced increased urine output or transient decrease in SCreat may not offer substantial renoprotection, and is only a part of the complex management strategy in AKI.

Conclusion

Several meta-analyses of diuretics in the management of AKI could not show improvements in mortality or rate of independence from RRT.[20,55,56] Diuretics increased the risk for contrast-induced AKI[57] and had no significant effect on mortality or creatinine clearance, but increased the incidence of AKI and need for RRT in cardiac surgery patients.[58] Both the European Society of Intensive Care Medicine and the Kidney Disease Improving Global Outcomes have since recommended that diuretics should not be used to prevent or treat AKI, except in the management of volume overload.[59,60] Fluid balance is an important predictor of adverse outcomes in critically ill patients, and diuretics have an important role in volume management. However, their use has to be balanced with timely initiation of RRTs. The currently approved diuretics for clinical use have a narrow, but important role in the management of AKI. The expert use of diuretics should be based on specific clinical situations, with a defined purpose and in the context of an understanding of the pathomechanisms involved.

Sidebar

Key Points

- Diuretics are not recommended for the prevention or treatment of AKI.
- Diuretics increase the risk of AKI.
- Forced diuresis for the prevention of AKI may be harmful because of the risk of volume overload.

- Diuretics have an important role in maintaining fluid balance.
- There is an evolving role for mineralocorticoid receptor blockade in preventing progression to CKD.

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Conflicts of interest

There are no conflicts of interest.

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