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# Overview of Diuretic Strategies in Edematous States

Kedar Mahajan, MD

*Thomas Jefferson University Hospitals, Kedar.Mahajan@jefferson.edu*Follow this and additional works at: <https://jdc.jefferson.edu/tmf> Part of the [Medicine and Health Sciences Commons](#)[Let us know how access to this document benefits you](#)

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# OVERVIEW OF DIURETIC STRATEGIES IN EDEMATOUS STATES

Kedar Mahajan, MD

## Introduction

Considering potential physiologic causes of volume overload in clinical practice, such as heart failure, renal failure, nephrotic syndrome, or portal hypertension, may yield insight into directing therapy beyond switching from oral to intravenous diuretic therapy. Appropriate oral therapies that achieve effective diuresis may reduce costs, address shortages of intravenous loop diuretics, reduce the need for unnecessary inpatient admissions by facilitating outpatient management, allow earlier optimization of outpatient regimens, and decrease the length of hospital stay.

## Congestive Heart Failure

Decreased responsiveness to oral diuretics in either high or low output heart failure has been described. Goldman's Cecil Medicine identifies factors such as gut edema, hypotension, reduced renal blood flow, and adaptive changes in the nephron.<sup>1</sup> Bowel wall edema from elevated systemic venous pressures in heart failure may decrease bioavailability of diuretics while increased renal afterload from venous congestion and intrinsic renal compromise from interstitial pressures impairs diuresis.<sup>2</sup> "Adaptive changes" are seen in long term loop diuretic use and include hypertrophy and hyperplasia of the distal convoluted tubule cells and increased Na<sup>+</sup>/Cl<sup>-</sup> - cotransporter activity which both contribute to increased sodium reabsorption.<sup>3</sup> This adaptation is partially addressed by blocking the reabsorption with thiazide/thiazide-like (e.g. hydrochlorothiazide or metolazone) diuretics and decreasing Na<sup>+</sup>/Cl<sup>-</sup> - cotransporter upregulation by inhibiting effects of aldosterone (e.g. spironolactone or eplerenone).<sup>1,3</sup>

Optimal outpatient management of diuresis in heart failure is often difficult. Doubling the oral dose of diuretics (furosemide, torsemide, and metolazone) does not affect left ventricular systolic or diastolic function, has been shown to improve symptoms and 6-minute walk distance after a 24 day endpoint.<sup>4</sup> Detrimental effects of high-dose diuretics in systolic dysfunction have been associated with increased mortality raising controversy, but confounding factors such as diuretic resistance or heart failure severity have made these links uncertain.<sup>5</sup> The superior pharmacodynamic profile of torsemide (see Table 1) and its anti-aldosterone and vasorelaxation effect likely contributes to its better performance in improving left ventricular function, reduction of mortality, frequency/duration of heart-failure related hospitalization, quality of life, exercise tolerance and New York Heart Association functional class compared with furosemide.<sup>6,7</sup> Synergy of loop-diuretics with potassium sparing or thiazide diuretics is efficacious in persistent edematous states.<sup>8</sup> Additionally, inadequate tissue perfusion, signaled by increasing

blood urea nitrogen or serum creatinine, can be addressed during diuresis in heart failure with inotropes or vasodilators.

## Renal Disease

Patients with renal insufficiency benefit from loop diuretics since they retain their utility at a creatinine clearance (CrCl) < 5 mL/min while distal tubule diuretics lose their efficacy at a CrCl < 40 mL/min. However, thiazides and thiazide-like diuretics (e.g. metolazone), provide synergistic effects when administered thirty min prior to a loop diuretic to inhibit compensatory distal tubular reabsorption, which avoids having to increase loop dosages and limits long-term exposure to high-dose diuretics.<sup>9,10</sup>

Higher doses of diuretics are required with a fall in the glomerular filtration rate, whether in chronic kidney disease (CKD), acute kidney injury, or hypoperfusion states. Drug secretion into the lumen of the nephron is diminished with retention of competing anions in renal failure and fewer functioning nephrons limit the maximal response of the drug. Moderate CKD can require 80 mg of intravenous furosemide (or bumetanide 2-3 mg, or torsemide 20-50 mg) while 200 mg may be required with severe CKD (or bumetanide 8-10 mg, or torsemide 50-100 mg).<sup>11</sup>

Renal tubular secretion of furosemide is typically normal in nephrotic syndrome but since the diuretic is bound to urinary albumin, the lack of active drug blunts the diuretic response. If urinary albumin exceeds 4 g/L, 50-66% of the drug is bound to albumin and inactive.<sup>12</sup> Appropriate measures include increasing doses, frequency, and using thiazides in conjunction with loop-diuretics. Avoidance of renal vasoconstriction mediated by non-steroidal anti-inflammatory drugs (NSAIDs) also improves diuretic responsiveness.

## Portal Hypertension

Limited cardiac output in heart failure decreases loop diuretic secretion into the tubular lumen from decreased renal perfusion, while cirrhosis through renal vasoconstriction. The mainstay diuretic in managing moderate-volume ascites in cirrhosis is either spironolactone (50-200 mg/day) or amiloride (5-10 mg/day) with low doses of furosemide (20-40 mg/day) to supplement natriuresis if peripheral edema is present. The recommended daily weight loss in these patients without and with peripheral edema is up to 1 lb and 2 lbs respectively to prevent pre-renal failure.<sup>13</sup> Patients with large-volume ascites and marked abdominal discomfort impairing activities of daily living can ideally undergo therapeutic paracentesis or attempt maximum doses of spironolactone (400 mg/day) and furosemide (160 mg/day). These patients typically present with urinary sodium

**Table 1. Pharmacodynamics and kinetics of common diuretics**

	Onset (min)	Peak (hours)	Duration (hours)	$\tau_{1/2}$ (hours)	Bioavailability (%)
Furosemide (PO)	30 – 60	1 – 2	6 – 8	0.5 – 2*	47 – 64
Furosemide (IV)	5		2		
Bumetanide (PO)	10	1	4 – 6	1 – 1.5	59 – 89
Torsemide (PO)	60	1 – 2	6 – 8	3.5†	80
Ethacrynic acid (PO)	30	2	12	2 – 4	
Metolazone (PO)	60		≥ 24	20	
Spirolactone (PO)		3 – 4	48-72	1.3‡	

\* End-stage renal disease: half-life ( $\tau_{1/2}$ ) increases to 9 hours

† Cirrhosis: half-life ( $\tau_{1/2}$ ) increases to 7-8 hours

‡ Active metabolites have the following half-lives ( $\tau_{1/2}$ ): canrenone: 10-23 hours; 7- $\alpha$ -spiro lactone: 7-20 hours

Loop diuretic equivalency: furosemide 40 mg PO = furosemide 2 mg IV = bumetanide 1 mg PO/IV = torsemide 20 mg PO/IV = ethacrynic acid 50 mg PO (sulfonamide alternative)

(Adapted from Lexi-Comp)

< 10 mM and normal free-water excretion and serum sodium. When free-water excretion is impaired, dilutional hyponatremia develops spontaneously or with increased fluid intake.

Patients with anasarca can have 2-3 L of fluid removed daily without reduction in plasma volume whereas patients with isolated ascites (no peripheral edema), can only have 300-500 mL/day of ascitic fluid mobilized daily without risking azotemia.<sup>14</sup> The azotemia will improve after ceasing diuresis and fluid repletion whereas hepatorenal syndrome, often mistakenly linked to diuretic use, will continue to worsen. Similar to patients in acute or chronic heart failure, rapid diuresis in cirrhotic patients leads to decreased cardiac output. Diuretic-resistant ascites is defined by either inability to mobilize ascites despite sodium restriction (24-hour urine with < 78 mEq sodium or a random urine sodium < urine potassium) and maximum oral diuretics (spironolactone 400 mg/day and furosemide 160 mg/day) or prohibitive diuretic-related complications (progressive azotemia, hepatic encephalopathy, or progressive electrolyte imbalance) in the absence of NSAIDs.<sup>15</sup> Ceasing beta-blockers, angiotensin receptor blockers, or angiotensin converting enzyme inhibitors, can improve blood pressure, tissue perfusion, renal function, and diuretic responsiveness.

## Discussion

Compounding renal insufficiency with reduced intestinal motility, perfusion, mucosal edema and tolerance to oral diuretics may also project a need for intravenous therapy; however, awareness of the pharmacokinetics and dynamics of diuretics will often provide solutions.<sup>16</sup> All diuretics need to attain a minimal rate of tubular excretion before a response is attained. Minimal response at a given dose indicates the dose was effective in achieving the minimal rate but the effect was

short-lived; a twice daily regimen can achieve the desired urine output. However, no response following a diuretic suggests doubling the dose (maximum furosemide dose 320-400 mg PO or 160-320 mg IV) for diuresis.<sup>11</sup> Between the minimum drug excretion rate required for initiating diuresis and a plateau where further drug excretion does not produce additional output, lies the critical curve where drug excretion correlates to the extent of natriuresis.

Tolerance exists even with consecutive multiple intravenous doses of furosemide in healthy individuals where natriuresis/diuresis decreases with compensatory increased renin and decreased atrial natriuretic peptide.<sup>17</sup> Outpatient diuretic tolerance can be compounded by renal compensatory mechanisms or an impaired natriuretic response to furosemide if on a low sodium diet.<sup>18</sup> A few weeks of a diuretic dose will activate sodium retaining forces (e.g. renin-angiotensin II-aldosterone, norepinephrine, or reduction in system blood pressure) to achieve steady-state in sodium intake and excretion.<sup>19</sup> However, poor adherence to sodium restriction on the other hand will prevent net fluid loss despite adequate diuresis; greater than 100 mEq sodium (2 g sodium = 88 mEq) in a 24-hour urine collection suggests non-compliance.<sup>20</sup>

Approaches that use higher doses of the drug, increased frequency, or synergy with other diuretics are required to overcome sodium retention. Substantial responses in diuretic naïve patients are likely due to a lack of these adaptations. Acute decompensated patients on outpatient doses of furosemide doses ≥ 120 mg/day benefit from initial bolus doses inpatient while outpatient regimens with lower doses responded better to initial continuous dosing.<sup>21</sup> Other loop diuretics such as bumetanide and toremide boast of superior bioavailability (Table 1) and can be considered first-line agents over furosemide in certain cases. In heart failure patients, toremide has been shown to decrease left-ventricular remodeling, rates of hospitalization,

and mortality over furosemide.<sup>6</sup> When compared to furosemide, bumetanide was more effective in reducing edema in patients with nephrotic syndrome and dyspnea in heart failure.<sup>6</sup> Certain localized edematous states secondary to venous insufficiency, moderate-severe lymphedema, or malignant ascites require caution against depleting plasma volume when using diuretics.<sup>14</sup>

Given the multifactorial causes of diuresis failure, exploring the nature of the edema state, utilizing a different diuretic agent or considering an additional agent, changing the route, frequency (Table 1), or the dose, can be attempted. The bioavailability of a diuretic will influence the dose required for a response while the plasma half-life will determine frequency of administration.

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