Management of loop diuretic resistance in the intensive care unit

Kwame Asare

Volume overload, a common complication of fluid resuscitation, is frequently encountered in the intensive care unit (ICU) and is associated with numerous adverse effects, including pulmonary and peripheral edema, acute lung injury, and pleural effusions. Loop diuretics are potent drugs used to treat volume overload and acute renal failure and to ameliorate their associated complications. These agents act at the thick ascending limb of the loop of Henle and inhibit the active transport of sodium and chloride out of the tubule lumen. Loop diuretics, which include furosemide, torsemide, bumetanide, and the less commonly used ethacrynic acid, produce a potent natriuresis and diuresis by blocking the reabsorption of the majority of filtered sodium. They reach their site of action by binding to serum proteins, notably albumin, and are then actively secreted into the urine at the straight segment of the proximal tubule.

Diuretic resistance

The administration of loop diuretics to hypervolemic or oliguric patients in the ICU is a relatively common clinical practice. Of the loop diuretics, furosemide is the most commonly used and is almost always administered intravenously in the ICU, with its dosage generally adjusted to reach a urine output goal of 0.5–1.0 mL/kg/hr. In a large, multicenter, multinational, observational study of more than 1700 ICU patients, about 70% of patients were reported to receive diuretics at the time of the study, with furosemide

Purpose. The management of loop diuretic resistance in the intensive care unit (ICU) is reviewed.

Summary. Volume overload, a common complication of fluid resuscitation, is frequently encountered in the ICU and is associated with numerous adverse effects, including pulmonary and peripheral edema, acute lung injury, and pleural effusions. Loop diuretics are used to treat volume overload and acute renal failure and to ameliorate their associated complications. When administered intravenously, these drugs induce vigorous and prompt diuresis, which may result in negative fluid balance. This may also result in significant adverse effects, including electrolyte imbalance, ototoxicity, and volume contraction. Prolonged use of loop diuretics may lead to loop diuretic resistance, a frequent observation in the ICU. Three general mechanisms are used to explain loop diuretic resistance: rebound sodium retention, postdiuretic effect, and diuretic braking. While very few agents have joined the armamentarium and no new strategies have been developed to deal with this phenomenon, several options are available to clinicians for managing loop diuretic resistance, including salt restriction, administration of i.v. loop diuretics, continuous infusion of loop diuretics, and combination therapy using loop diuretics and thiazides.

Conclusion. Loop diuretic resistance presents a challenge for clinicians in the ICU setting. Strategies to improve patients’ responsiveness to these agents include fluid and salt restriction, switching from oral to i.v. loop diuretics, increasing diuretic dose, continuous infusion, and combination therapy with thiazides. Several of these strategies may be used concurrently to combat diuretic resistance and promote symptomatic relief of edema in the critically ill patient.

Index terms: Critical illness; Diuretics; Dosage schedules; Drug administration; Edema; Hospitals; Resistance; Toxicity

The Clinical Consultation section features articles that provide brief advice on how to handle specific drug therapy problems. All articles are based on a systematic review of the literature. The assistance of ASHP’s Section of Clinical Specialists and Scientists in soliciting Clinical Consultation submissions is acknowledged. Unsolicited submissions are also welcome.

Loop diuretic resistance

The second mechanism is post-diuretic effect, a compensatory sodium-retention process that begins as the diuretic action wanes. Technically, postdiuretic sodium retention is not diuretic resistance, since the diuretic is producing the expected effect. The body has compensated by absorbing more sodium, partially nullifying the effect of the drug.

The third mechanism is “diuretic braking,” the decrease in a patient’s response to a diuretic after receiving the first dose. In other words, the magnitude of response to each administered dose of diuretic declines with time. For example, the diuretic response of furosemide reportedly falls by as much as 40% by the third day of treatment, depending on the degree of volume depletion. Some clinicians argue that diuretic braking is not a separate mechanism but occurs as a result of the first and second mechanisms. Diuretic resistance may occur as a result of a combination of these mechanisms and is believed to protect the patient from intravascular volume and sodium depletion. Understanding these mechanisms is paramount to reduce diuretic resistance and thereby improve the efficacy of loop diuretics.

Therapeutic strategies to manage diuretic resistance

Salt restriction. Dietary sodium restriction is a key determinant of diuretic efficacy. When dietary sodium intake is high, postdiuretic sodium retention compensates almost entirely for the loop-diuretic-induced sodium loss. Conversely, if sodium intake is restricted, postdiuretic sodium retention is minimized, resulting in a negative fluid and sodium balance. Hence, most edematous patients can be treated successfully by dietary sodium restriction. This approach is usually not applicable to critically ill patients, since the majority of them receive no dietary sodium.

I.V. diuretics. Sometimes, administering diuretics intravenously instead of orally is all that is required to improve diuresis, especially in critically ill patients with significant renal dysfunction. Absorption of orally administered loop diuretics in this patient population may be altered in the presence of gastrointestinal edema, gastroparesis, and delayed gastric emptying. Furthermore, there is inadequate drug concentration at the site of diuretic action in the tubule lumen. This may be due to decompensated heart failure, renal hypoperfusion, or impaired secretion as a result of hypoalbuminemia, a common occurrence in critically ill patients. Vasco et al. found, in a study of 11 patients, that furosemide absorption was altered in patients with decompensated congestive heart failure.

Furosemide has a bioavailability of about 50%; thus, converting from an oral to i.v. dose is equivalent to doubling the oral dose. For example, 40 mg of furosemide administered intravenously produces twice the effect as 40 mg given orally. Torsemide and bumetanide, on the other hand, have almost complete absorption (80–100%), resulting in equivalent oral and i.v. doses.

Continuous infusion. Limited data from small heterogeneous studies suggest that continuous infusions are more effective than bolus doses for improving diuresis. Continuous administration of diuretics, which limits the effect of postdiuretic sodium retention, has been shown to improve diuresis in many ICU patients with refractory edema without serious adverse effects. It may decrease the fluctuations in intravascular volume, resulting in a more gradual and relatively constant hourly urine output, which mimicks physiological urinary output.

In a prospective, randomized, crossover study, Lahav et al. compared intermittent i.v. administration of furosemide with continuous infusion after a loading dose in nine patients with severe heart failure. At the time of hospital admission, patients were randomly assigned to one of two treatment groups. The dose of furosemide was equivalent in both groups. After 48 hours, each

being the diuretic of choice 98% of the time. Most critical care clinicians are familiar with the administration, pharmacology, and adverse effects of loop diuretics. However, not all are familiar with the mechanisms associated with loop diuretic resistance and its management.

In some critically ill patients, conventional doses of loop diuretics do not always result in optimal diuresis. In such cases, patients are considered “diuretic resistant.” Three mechanisms of the phenomenon of diuretic resistance have been suggested. The most common is the concept of rebound sodium retention. After administration of loop diuretics, sodium absorption is blocked at the loop of Henle, leading to a pronounced reabsorption of sodium at the distal sites of the nephron. This reabsorption may be sufficient to nullify the prior blockade. Studies in rats have shown that six to eight days of continuous furosemide infusion caused hypertrophy of the distal convulated tubule, the connecting tubule, and the collecting ducts of the nephron. This results in an enhanced capacity for sodium and fluid reabsorption by the hypertrophied distal tubule. This explains the synergistic response to combination therapy (using a loop diuretic and a thiazide to block sodium reabsorption at the loop of Henle and the distal tubule, respectively). The second mechanism is post-diuretic effect, a compensatory sodium-retention process that begins as the diuretic action wanes. Technically, postdiuretic sodium retention is not diuretic resistance, since the diuretic is producing the expected effect. The body has compensated by absorbing more sodium, partially nullifying the effect of the drug.

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patient crossed over to the other treatment group and was treated for an additional 48 hours. Continuous infusion produced significantly greater diuresis and natriuresis than intermittent i.v. administration; total urine output increased by 12–26%, and total sodium excretion increased by 11–33% ($p < 0.01$).

In another study, 20 surgical ICU patients were randomized to receive furosemide by continuous infusion ($n = 10$) or intermittent bolus injection ($n = 10$). The group receiving the continuous infusion demonstrated a significantly greater mean ± S.D. daily urine volume compared with the group receiving the bolus injection (2860 ± 240 mL versus 2260 ± 150 mL, respectively; $p = 0.0005$). The authors did not provide the dose of furosemide used, and no information regarding demographics of the two groups was provided.

Other published reports have revealed better diuresis and natriuresis with continuous infusions of loop diuretics compared with medium and high bolus doses. In a randomized, unblinded study, Osterman and colleagues compared the efficacy of a continuous infusion of furosemide with that of intermittent bolus doses. Fifty-nine critically ill adult patients were randomized to either treatment group according to predefined algorithms. There was no significant difference in diuretic response between the two groups, but a significantly higher dose of furosemide was needed to achieve target diuresis in patients receiving intermittent bolus doses (24.1 mg/hr versus 9.2 mg/hr, $p = 0.0002$). Mean urine output per dose of furosemide was significantly higher in patients receiving furosemide as a continuous infusion (31.6 mL/mg versus 18 mL/mg, $p = 0.014$). At the end of the study, no significant differences in hospital mortality, number of patients requiring ventilatory support, or change in serum creatinine levels were found between groups.

Interestingly, there was no significant difference in adverse effects between the groups, despite the differences in dosages used. The authors concluded that furosemide administered as a continuous infusion was more effective than intermittent bolus doses, since significantly less furosemide was required to produce the same diuresis.

Not all studies have found the superiority of continuous infusion over intermittent loop diuretic therapy. Schuller and colleagues conducted a prospective, randomized, comparative, protocol-driven study to evaluate the safety and relative efficacy of two diuretic protocols in the ICU. They randomized 33 cardiac and medical patients to treatment with a continuous infusion of furosemide or bolus dosing. All patients received a 40-mg i.v. bolus dose. Patients receiving the continuous infusion were then started on furosemide 0.1 mg/kg/hr, which was increased hourly to a maximum of 0.75 mg/kg/hr. Patients treated with bolus doses of furosemide received double the previous dose if renal output was less than 1 mL/kg/hr within 1–2 hours of receiving the last dose. If renal output was greater than 1 mL/kg/hr, the previous dose was repeated in 4–6 hours. Both regimens were equally effective in achieving a negative fluid balance. The authors reported no symptomatic evidence of ototoxicity in either group, though a small but statistically significant increase in serum creatinine levels was observed in patients receiving bolus doses of furosemide (no $p$-values were reported). This study had several limitations, the most significant of which was the study’s 72-hour duration, making it difficult to extrapolate the results to longer durations of treatment. Since diuretic braking and postdiuretic effect (the major reasons for continuous infusion therapy) become increasingly significant with time, 72 hours of diuretic therapy may not be long enough to determine any difference between continuous and intermittent therapy.

Another study found no significant difference in the diuretic or natriuretic effects of the two modes of administration in adult patients who had undergone open heart surgery. However, because patient demographics were not disclosed, it is difficult to determine if both groups were similar in terms of severity of illness and other confounding variables.

Despite the conflicting evidence, pharmacodynamic concepts support the improved efficacy of continuous infusion of all loop diuretics except ethacrynic acid. Continuous infusion offers many advantages, including elimination of a diuretic-free interval (during which compensatory sodium retention occurs) and a decreased rate of adverse effects. The decreased rate of adverse effects may be due to the lower peak drug concentration during continuous infusion. Interestingly, the total dose of furosemide in almost all studies has been lower in patients receiving continuous infusion versus intermittent bolus doses.

A bolus dose of a loop diuretic should be administered before initiating a continuous infusion or when the infusion rate is increased in order to decrease the time for the drug's onset of action (Figure 1). In a previously mentioned study in which a loading dose was not given, the onset of diuresis occurred approximately three hours after initiation of the continuous infusion. The recommended loading dose and initial infusion rate are usually determined by the patient's renal function (Table 1).

**Combination therapy.** One approach that is remarkably effective for managing diuretic resistance is sequential blockade of the nephron. This is done by combining diuretics that act in different segments of the nephron, usually a loop and a thiazide diuretic, resulting in inhibition of reabsorption at multiple sites. This phenomenon of diuretic...
synergism is well documented in the literature.25-31 Loon et al.25 examined the possible mechanisms of diuretic braking in patients with mild-to-moderate essential hypertension who were treated with furosemide. They found evidence of an increase in sodium reabsorption at the distal convoluted tubule, the site of action of thiazide diuretics. The authors suggested that this observation may provide a rationale for the use of thiazide and loop diuretic combinations in the treatment of severe edema resistant to high doses of loop diuretics alone. In another study of mildly azotemic hypertensive patients, Wollam et al.27 found that doubling the dose of furosemide had little effect on patients’ body weight, blood pressure, and serum creatinine level, demonstrating loop diuretic resistance. However, the addition of hydrochlorothiazide to furosemide therapy normalized the blood pressure and resulted in substantial weight loss. Fliser and colleagues31 found that thiazide diuretics markedly increased the efficacy of loop diuretics, even in patients with advanced renal failure. The authors used excretion of sodium and chloride as markers of efficacy. The clinical importance of this measure is unclear; nonetheless, their finding contrasts with the recommendation to withhold thiazides in such patients because of their assumed lack of efficacy.24,29

Metolazone and hydrochlorothiazide are the two thiazides most commonly used in combination with a loop diuretic. Although each of these thiazides has its pharmacokinetic advantage, there is no clear evidence that one is superior to the other. Some clinicians prefer metolazone because of its efficacy in advanced renal failure, a setting in which other thiazides have been reported to be less effective.32 However, the study that led to this conclusion used very high doses of metolazone (20–150 mg),32 and it is likely that other thiazides may have a similar effect when used in equivalent doses.33 When initiating combination therapy, the thiazide should be administered before the i.v. loop diuretic to allow enough time for full blockade of the distal nephron before it is flooded

<table>
<thead>
<tr>
<th>Agent</th>
<th>Loading Dose</th>
<th>Initial Infusion Rates (mg/hr) Based on Creatinine Clearance</th>
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<tbody>
<tr>
<td></td>
<td>Initial Dose</td>
<td>Maximum Dose</td>
</tr>
<tr>
<td>Furosemide</td>
<td>40 mg</td>
<td>200 mg</td>
</tr>
<tr>
<td>Bumetanide</td>
<td>1 mg</td>
<td>5 mg</td>
</tr>
<tr>
<td>Torsemide</td>
<td>20 mg</td>
<td>100 mg</td>
</tr>
<tr>
<td>Ethacrynic acid</td>
<td>0.5 mg/kg</td>
<td>100 mg</td>
</tr>
</tbody>
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*aShould not be used as continuous infusion. NA = not applicable.
with sodium from the thick ascending limb. This staggered dosing is not necessary when oral loop diuretics are administered.

Combination therapy has some advantages. First, it minimizes the hypocalcemia caused by loop diuretics due to the anticalciuric action of thiazide diuretics. Second, because of the long half-lives of thiazide diuretics, the duration of action of thiazides outlasts that of intermittent administration of loop diuretics and thus prolongs the overall natriuresis and diuresis. However, combination therapy is associated with a significant increase in adverse effects over either therapy alone and requires careful monitoring. For this reason, it is preferable to use escalating doses of loop diuretics up to the maximum recommended doses and to reserve combination therapy for the occasional patient with high resistance to loop diuretics.

Adverse effects

Unfortunately, adverse consequences were reported in 11 of 17 articles reviewed by Oyster et al. The most common adverse effects of loop diuretics are intravascular volume depletion, hypotension, electrolyte disorders, and metabolic alkalosis. The electrolytes most affected are sodium, potassium, magnesium, and calcium. Massive fluid and electrolyte losses may lead to hypotension or circulatory collapse, especially in critically ill patients with vasodilatory shock. Loop diuretics may also cause ototoxicity, especially in patients receiving both high doses and other ototoxic drugs (e.g., aminoglycosides). Ototoxicity is related more to high peak concentrations than to the total amount of drug given. To minimize ototoxicity, a continuous infusion rather than high bolus doses is recommended. Clinicians are also advised not to exceed an infusion rate of 4–6 mg/min of furosemide; similar recommendations with other loop diuretics are lacking.

Ethacrynic acid has the greatest ototoxic potential and torsemide has the least; hence, ethacrynic acid is usually given to sulfa-allergic patients who have reactions to other loop diuretics. However, a large prospective cohort study suggested that patients with a history of sulfonamide antibiotic allergy can tolerate nonantibiotic sulfonamides. Torsemide has aldosterone antagonist activity in animal models and can theoretically contribute to hyperkalemia in patients with renal insufficiency; however, this has not been seen in clinical practice.

Conclusion

Loop diuretic resistance presents a challenge for clinicians in the ICU setting. Strategies to improve patients’ responsiveness to these agents include fluid and salt restriction, switching from oral to i.v. loop diuretics, increasing diuretic dose, continuous infusion, and combination therapy with thiazides. Several of these strategies may be used concurrently to combat diuretic resistance and promote symptomatic relief of edema in the critically ill patient.

References