The Effect of Add-on Acetazolamide to Conventional Diuretics for Diuretic-resistant Edema Complicated with Hypercapnia: A Report of Two Cases

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Abstract:
We herein report two cases in which add-on acetazolamide to furosemide was effective for diuretic-resistant volume overload and hypercapnia. Case 1 was a woman in her 40s presenting with volume overload due to the nephrotic syndrome with diabetes mellitus. Case 2 was a man in his 60s with fluid overload and non-nephrotic proteinuria and sepsis. In both cases, although fluid overload was resistant to high-dose loop diuretics and complicated with hypercapnia due to pulmonary effusion, add-on acetazolamide administration resulted in symptom resolution. The additional effect of acetazolamide occurred regardless of the degree of proteinuria and kidney function.

Key words: diuretics, diuretic resistance, hypercapnia, acetazolamide

Introduction
Although loop diuretic is effective for volume overload, we often experience diuretic-resistant cases in which an increasing dose of loop diuretic fails to improve volume overload and results in worsening hypercapnia due to pleural effusion. Because the increased sodium reabsorption in segments other than the thick ascending limb contributes to resistance to loop diuretics, the combination of diuretics that have an effect on sites other than the thick ascending limb is thought to be effective theoretically. Although combinations of thiazide or tolvaptan with loop diuretics are known to be effective (1, 2), both loop diuretics and thiazide often result in the elevation of bicarbonate. Under conditions of insufficient ventilation, elevated bicarbonate can be a risk factor for further compensated respiratory depression, especially hypercapnia. Therefore, add-on thiazide use may not be the best option for treating patients with hypercapnia who develop resistance to loop diuretics. Acetazolamide inhibits carbonic anhydrase and reduces the reabsorption of sodium ion (Na⁺) in the proximal tubule. The decreased sodium reabsorption can be surpassed by increased sodium reabsorption in the downstream nephron segments, such as the loop of Henle, distal convoluted tubule, and cortical collecting duct. Therefore, acetazolamide use itself has been considered a weak diuretic. Recently, several reports of animal experiments, in which acetazolamide was combined with other diuretics, showed its significant diuretic effect in cases with diuretic-resistant volume overload (3-5). A recently published randomized trial among patients with nephrotic syndrome showed a significant diuretic effect in cases with diuretic-resistant volume overload (6). Furthermore, acetazolamide can improve metabolic alkalosis or decrease bicarbonate and sequentially improve hypercapnia, as acetazolamide inhibits reabsorption of bicarbonate (HCO₃⁻) in the proximal tubule. We herein report two cases (one with and one without nephrotic syndrome and kidney dysfunction) of diuretic (mainly furosemide)-resistant volume overload with hypercapnia in which acetazolamide added on to furosemide resulted in significant salutary ef-
### Table 1. Laboratory Data in Case 1.

|                  | X+20d | X+50d | X+5m | X+6m | X+7m | X+8m | X+9m |
|------------------|-------|-------|------|------|------|------|------|
| Dose of Acetazolamide, mg started | 200   | 120   | 120  | 120  | 80   | 120  | 120  |
| Dose of Furosemide, mg re-started | 200   | 120   | 120  | 120  | 80   | 120  | 120  |
| Urinary protein excretion (mg/gCr), X | 9,985 | 6,603 | 11,965 | 5,434 | 4,834 | 7,711 | 5,273 |
| Albumin (g/dL) | 3.1   | 3.1   | 2.2  | 2.7  | 2.9  | 2.9  | 2.8  |
| Serum creatinine (mg/dL) | 1.76  | 2.00  | 1.86 | 1.95 | 2.02 | 1.94 | 2.14 |
| eGFR (mL/min/1.73 m²) | 26.4  | 23.0  | 24.7 | 23.5 | 22.6 | 23.6 | 21.2 |
| BUN (mg/dL)    | 57.1  | 55.6  | 33.6 | 52.6 | 60.0 | 41.7 | 51.3 |
| Na (mEq/L)     | 143   | 140   | 142  | 142  | 142  | 142  | 141  |
| K (mEq/L)      | 4.4   | 4.2   | 4.3  | 4.7  | 4.8  | 5.4  | 4.7   |
| Cl (mEq/L)     | 101   | 105   | 108  | 110  | 108  | 116  | 112   |
| Na-Cl (mEq/L)  | 42    | 35    | 34   | 32   | 34   | 28   | 29    |
| Uric acid (mg/dL) | 5.9  | 7.3   | 5.8  | 6.3  | 7.3  | 6.3  | N/A   |
| Venous blood gas |       |       |      |      |      |      |       |
| pH              | 7.293 | 7.293 | 7.367 | 7.313 | 7.299 | 7.286 | 7.314 |
| PCO₂ (mmHg)     | 67.5  | 48.9  | 48.1 | 46.2 | 46.9 | 46.3 | 38.8  |
| HCO₃⁻ (mmol/L)  | 31.7  | 22.9  | 26.9 | 22.7 | 22.3 | 21.4 | 19.1  |
| Corrected HCO₃⁻ (mmol/L) | 36.4 | 28.0 | 27.6 | 26.8 | 27.1 | 26.8 | N/A   |
| Body weight (kg) | 72.2  | 64.0  | 75.6 | 68.0 | 67.5 | 70.0 | 71.9  |

*d*: days, *m*: months, eGFR: estimated glomerular filtration rate, BUN: blood urea nitrogen, Na: sodium, K: potassium, Cl: chloride, PCO₂: partial pressure of carbon dioxide, HCO₃⁻: bicarbonate, N/A: not available

The corrected HCO₃⁻ was calculated as 24 (normal HCO₃⁻)+ΔPCO₂×0.45 in accordance with the previous literature (12)

X: date of discharge prior to the present clinical course

### Figure 1. Clinical course of case 1. We used acetazolamide twice in patients with nephrotic syndrome resistant to several diuretics. X: date of discharge prior to the present clinical course, d: days, m: months

A woman in her 40s with diabetes mellitus for 2 years

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**Case Presentation**

**Case 1 (Table 1 and Fig. 1)**

A woman in her 40s with diabetes mellitus for 2 years...
presented with leg edema, for which furosemide (40 mg/day) was prescribed. However, she developed nephrotic syndrome, notable weight gain (from 76.7 to 98.4 kg), and pulmonary effusion. The diagnosis was fluid overload due to nephrotic syndrome with diabetic nephropathy. She took nifedipine, febuxostat, and atorvastatin for each metabolic complication. Renin-angiotensin-aldosterone (RAA) system blockers were not prescribed during this clinical course. However, although she was placed on salt restriction and treated with an increasing dose of furosemide up to 200 mg/day, the fluid overload was difficult to control, so she was admitted. At this point, the cardiac and liver function was normal. Tolvaptan (15 mg/day) and consequently spironolactone (12.5 mg/day) as well as trichlormethiazide (2 mg/day) were started. The fluid overload resolved (from 98.4 to 68.7 kg), and she was discharged (day X in Fig. 1). However, 3 months, eGFR: estimated glomerular filtration rate, BUN: blood urea nitrogen, Na: sodium, K: potassium, Cl: chloride, PCO2: partial pressure of carbon dioxide, HCO3−: bicarbonate, N/A: not available The corrected HCO3− was calculated as 24 (normal HCO3−)+ΔHCO3−/0.45 in accordance with the previous literature (12)

Table 2. Laboratory Data in Case 2.

|                  | X+30d | X+32d | X+35d | X+40d | X+45d | X+47d |
|------------------|-------|-------|-------|-------|-------|-------|
| Dose of Acetazolamide, mg started | 250 | 250 | 250 | 125 | 125 |
| Dose of Furosemide, mg | 60 | 60 | 60 | 60 | 60 |
| Albumin (g/dL) | 1.8 | 1.9 | 1.8 | 2.0 | 2.1 | 2.2 |
| Serum creatinine (mg/dL) | 0.70 | 0.83 | 0.82 | 0.79 | 0.76 | 0.78 |
| eGFR (mL/min/1.73 m²) | 86.9 | 72.1 | 73.1 | 76.1 | 79.4 | 77.2 |
| BUN (mg/dL) | 11.6 | 12.8 | 14.1 | 15.8 | 16.9 | 14.8 |
| Na (mEq/L) | 139 | 140 | 138 | 137 | 139 | 138 |
| K (mEq/L) | 3.5 | 3.9 | 4.1 | 4.3 | 4.4 | 4.3 |
| Cl (mEq/L) | 96 | 100 | 105 | 108 | 105 |
| Na-Cl (mEq/L) | 45 | 40 | 33 | 32 | 31 | 33 |
| Uric acid (mg/dL) | 5.4 | N/A | N/A | N/A | N/A |
| Venous blood gas pH | 7.381 | 7.385 | 7.345 | 7.309 | 7.299 | 7.323 |
| PCO2 (mmHg) | 60.1 | 52.6 | 45.5 | 44.2 | 51.1 | 49.0 |
| HCO3− (mmol/L) | 34.9 | 30.8 | 24.1 | 21.5 | 24.3 | 24.7 |
| Corrected HCO3− (mmol/L) | 34.0 | 29.7 | 26.5 | 25.9 | 29.0 | 28.0 |
| Body weight (kg) | 69.2 | N/A | N/A | N/A | N/A |

- d: days, m: months, eGFR: estimated glomerular filtration rate, BUN: blood urea nitrogen, Na: sodium, K: potassium, Cl: chloride, PCO2: partial pressure of carbon dioxide, HCO3−: bicarbonate, N/A: not available
- The corrected HCO3− was calculated as 24 (normal HCO3−)+ΔHCO3−/0.45 in accordance with the previous literature (12)

Case 2 (Table 2 and Fig. 2)

A man in his 60s without a significant medical history developed leg edema and weight gain for 1.5 months and was admitted for the gradual progression of these symptoms. In addition to fluid overload, he had poorly controlled diabetes mellitus and methicillin-susceptible Staphylococcus aureus (MSSA) bacteremia caused by lower limb cellulitis. He took telmisartan and some sleeping pills during this clinical course. No dosage adjustment of telmisartan was observed. Along with the treatment for diabetes and cellulitis, furosemide (40 mg/day) was administered orally for fluid overload. His body weight decreased (approximately 17 kg) over 3 weeks, and he was discharged at his request (day X in Fig. 2). However, 10 days after discharge, weight gain (66.8 to 71.4 kg), exacerbation of pleural effusion, and MSSA bacteremia due to recurrent lower-limb cellulitis occurred. Examinations revealed urine protein of 1.06 g/gCr, venous blood gas of pH 7.375, HCO3−: 26.7 mmol/L, pCO2: from 22.9 to 26.9 mmol/L without elevation of pCO2, potentially leading to metabolic alkalosis; therefore, acetazolamide was resumed (250 mg/day). The excessive body fluid volume and increasing of bicarbonate without hypercapnia improved after restarting acetazolamide. After acetazolamide resumption, only mild metabolic acidosis (minimal HCO3−: 20.3 mmol/L at oral acetazolamide administration of 250 mg) was observed thereafter. Thus, the dose of acetazolamide was reduced to 125 mg, and the patient maintained her condition without excessive fluid, significant electrolyte abnormalities, or deterioration of the kidney function.
Figure 2. Clinical course of case 2. We used acetazolamide in a patient with furosemide-resistant non-nephrotic syndrome. X: date of discharge prior to the present clinical course, d: days, IV: intravenous injection, UV: urine volume

46.8 mmHg, and serum creatinine of 0.74 mg/dL, sodium of 146 mEq/L, potassium of 4.5 mEq/L, and chloride of 101 mEq/L. Although we started oral (40 mg/day) and intravenous (60 mg/day) furosemide after hospitalization, the weight reduction was poor, and a significant response was not observed, even after increasing the dosage of oral furosemide (60 mg/day). Furthermore, the compensatory elevation of bicarbonate significantly progressed (HCO₃⁻ 39.0 mmol/L), possibly because of the use of furosemide and hyperventilation due to pulmonary effusion. Therefore, acetazolamide (250 mg/day) was administered. At 10 days after starting acetazolamide, his body weight had decreased by 5.5 kg. Because hyperventilation and the consequent elevation of bicarbonate improved and became slightly overcorrected (HCO₃⁻ 21.5 mmol/L), the acetazolamide dose was reduced to 125 mg/day, after which fluid overload did not occur, and the acid-base balance improved to the normal range (24.7 mmol/L).

Discussion

We experienced two cases with loop diuretic-resistance volume overload complicated with hyperventilation due to pleural effusion and consequent elevation of bicarbonate in which add-on administration of acetazolamide to furosemide resulted in a significantly improved volume status and acid-base balance, regardless of complication with nephrotic syndrome or kidney dysfunction. Although we were unable to assess the arterial blood gas values to clearly evaluate the acid-base status in these present cases, we would like to emphasize that acetazolamide was found to be effective in the treatment of cases with both elevated carbon dioxide and bicarbonate levels, irrespective of their primary acid-base abnormalities, namely either primary respiratory acidosis or primary metabolic alkalosis. The diuretic resistance in both cases was attributed to poor adherence to salt intake restriction (case 1 was an outpatient, and case 2 was an inpatient who tended to sneak food), hypoalbuminemia causing an impaired delivery of loop diuretics (hypoalbuminemia was due to nephrotic syndrome in case 1 and inflammatory status in case 2), stimulation of the RAA system reducing the diuretic response, and renal congestion. The long-term and high-dose use of furosemide diuretics might lead to RAA system stimulation, which might enhance sodium reabsorption through the Na⁺/H⁺ exchanger in the proximal tubule, epithelial Na⁺ channel (ENaC) in the distal tubule, and pendrin. As with the other factors, the decrease in the glomerular filtration rate in case 1 and the temporary use of nonsteroidal anti-inflammatory drugs (7) might contribute to diuretic resistance. Acetazolamide inhibits the carbonic anhydrase and decreases the reabsorption of sodium bicarbonate in the proximal tubule. Decreasing bicarbonate can stimulate ventilation, so acetazolamide can be prescribed as an approved medication for respiratory acidosis due to hyperventilation, as in the present cases. Furthermore, the increased delivery of chloride (Cl⁻) decreases renin secretion, which results in a decreased RAA system effect. Even for patients without hyperventilation, acetazolamide is suitable for use in treating metabolic alkalosis with volume overload, since it enhances the diuretic effect by inhibiting the pendrin response in connecting tubules and cortical collecting ducts (5, 6, 8). The Cl⁻/HCO₃⁻ exchanger pendrin (SLC26A
Figure 3. Changes in urinary Na, Cl, and K excretions after acetazolamide administration in Case 2. Increases in urinary Na, Cl, and K excretions were observed after the administration of acetazolamide. X: date of discharge prior to the present clinical course, d: days, mEq/gCr: urinary electrolyte excretion creatinine ratio (estimation of daily excretion)

4) is located in the apical membrane of B intercalated cells in the connecting tubules and cortical collecting ducts. Pendrin secretes HCO₃⁻ and reabsorbs Cl⁻, and its work is enhanced in cases of metabolic alkalosis. Pendrin also enhances sodium reabsorption through the activation of the ENaC and Na⁺-driven anion-exchanger (9, 10). Therefore, the inhibition or downregulation of pendrin due to not only the correction of metabolic alkalosis but also the direct effect of acetazolamide results in decreased sodium reabsorption. Sodium reabsorptions of pendrin and NCC have a complementary relationship with each other, and some reports on the inhibition of pendrin and NCC have shown significant diuretic effects in animal experiments (3, 4, 11). The successful effects of acetazolamide in our two cases might be due to prior furosemide administration having enhanced the effect of furosemide following add-on acetazolamide administration. Although the dynamics of the RAA system before and after additional acetazolamide administration were not elucidated in these two cases, as we did not examine the RAA system titer, additional acetazolamide administration might improve the increased RAA system caused by increased furosemide use. The urinary excretion of sodium and chloride corrected by urine creatinine, estimation of daily excretion, using spot urine examination in case 2 is shown in Fig. 3. The urinary excretion of sodium and chloride decreased before the combined use of acetazolamide and increased after its administration, thus suggesting that the mechanisms of acetazolamide worked effectively in this case. To our knowledge, only one randomized controlled trial has shown the combination effect of acetazolamide for diuretic-resistant nephrotic syndrome (6). In the acetazolamide + hydrochlorothiazide (HCTZ) group, the urine volume was increased, and the body weight was decreased compared with the furosemide + HCTZ group. That study included only patients with nephrotic syndrome and a normal renal function. In contrast, combination with acetazolamide was effective in our cases with diuretic-resistant volume overload, even in the case with kidney dysfunction and mild proteinuria (case 2). One point of caution should be noted: patients with chronic kidney disease tend to have metabolic acidosis due to a decreased ability to excrete acid because of the decreased production of ammonia in the kidney. Therefore, with long-term use of acetazolamide, close follow-up to monitor the acid-base balance is necessary because of the increased risk of developing metabolic acidosis.

Conclusions

The add-on acetazolamide to furosemide might be effective, regardless of the extent of proteinuria and the renal function, in volume-overload patients with diuretic resistance, especially in those with concomitant hypercapnia and consequent elevation of the bicarbonate level.

The authors state that they have no Conflict of Interest (COI).

Human and animal rights

All procedures performed in the present cases involving hu-
man participants were in accordance with the ethical standards of the institutional and/or national research committee at which the studies were conducted and complied with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Informed consent

No information identifying the individual patients is included, and all personal information has been protected. The patients provided their informed consent for the publication of this case report.

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