Acetazolamide As A Valuable Addition to Acute Heart Failure?

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Consider IV Acetazolamide in addition to standard IV loop diuretic therapy in patients hospitalized for acute decompensated heart failure.[1] (J Am Board Fam Med 2024;37:351–353.)

Keywords: **Acetazolamide, Cardiologists, Edema, Heart Failure, Left, Pleural Effusion, Patient Readmission, Ventricular Function**

STRENGTH OF RECOMMENDATION: B
Based on a single randomized controlled trial.[1]

Illustrative Case

A 54 year-old man with a history of heart failure with reduced ejection fraction presents to the hospital for acute decompensated heart failure. At baseline, he is on 40 mg of oral lasix and he has been taking this with no improvement in his symptoms. He was previously hospitalized for acute decompensated heart failure and was discharged at a weight higher than during his admission. He reports that after discharge, he still felt "extra fluid" but had improved since admission. What can you offer as treatment during this hospitalization in addition to standard IV loop diuretic therapy?

Clinical Context

Heart failure is among the most common causes for hospitalizations, leading to over 1 million hospitalizations a year. In addition, the mortality of heart failure is high with an in-hospital mortality of 3.8% and is mentioned on 1 in 9 death certificates in the United States.[2,3] Volume overload is associated with increased mortality.[4] In addition, in-hospital weight loss has been shown to be a marker of successful diuresis and decongestion and is associated with decreased mortality and hospital readmission.[5] Despite this, patients are often discharged from the hospital with an increase in body weight.[6]

While there are no randomized controlled trials (RCTs) comparing loop diuretics to placebo due to presumed superiority, they are the preferred diuretic agents in heart failure per guidelines.[7] Other diuretics such as metolazone, chlorothiazide and tolvaptan have been shown to increase weight loss when used in tandem with loop diuretics.[8]

Acetazolamide is a carbonic-anhydrase inhibitor diuretic that has not previously been studied extensively in patients with heart failure. However, it has similar efficacy as other diuretic combinations such as thiazide-loop-diuretic combinations. In addition, it has the benefit of reducing serum bicarbonate and can be used to balance metabolic alkalosis such as in the case of alkalosis induced by loop diuretics.[9] The trial discussed here is a randomized controlled, prospective study that investigates the combination of acetazolamide with a loop diuretic in treating acute decompensated heart failure in hospitalized patients.

Methods

This article was identified as a potential PURL through the standard systematic methodology.[10]

This article was externally peer reviewed.
Submitted 18 October 2023; accepted 19 October 2023.
From the UPMC St. Margaret Family Medicine Residency Program, Pittsburgh, PA.
Funding: None.
Conflict of interest: Dr. Ge has served as a consultant for CSL Seqirus.
FPIN Editor: Greg Castelli, PharmD, University of Pittsburgh Family Medicine, Pittsburgh, PA.
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Study Summary

This multi-center, double-blind, placebo-controlled randomized trial in Belgium compared intravenous acetazolamide to placebo when added to standard intravenous loop diuretics in patients hospitalized for acute decompensated heart failure who were on oral maintenance therapy of at least 40 mg of furosemide equivalent for 1 month prior as outpatients. All study participants had clinical signs of volume overload as well as NT-proBNP >1000 pg/mL or BNP >250 pg/mL. Clinical suspicion for pleural effusion or ascites was confirmed via radiograph or ultrasound. Patients were excluded if they received acetazolamide or another proximal tubular diuretic (ex. SGLT2 inhibitors) as maintenance therapy, had a systolic blood pressure <90mmHg, or an eGFR < 20 mL/min/1.73m^2. The maximum dose of intravenous furosemide allowed before randomization was 80 mg.

Patients were randomized 1:1 to treatment with 500 mg intravenous acetazolamide or placebo. Randomization was stratified based on whether they had a left ventricular ejection fraction of =<40% or >40%, as well as based on trial center. Interventions were administered with initial intravenous loop diuretic bolus as well as with the first dose of diuretic during the next 2 days. Loop diuretics were dosed at double the oral maintenance dose administered as a single bolus initially on randomization and then split into 2 doses on each of the next 2 days. In addition, all patients received a maintenance infusion of 500 mL 5% dextrose with 3g of magnesium sulfate per 24 hours. Treatment was escalated if urinary output was less than 3.5L over 30 to 48 hours and signs of fluid overload was present.

The primary end point was successful decongestion within 3 days. This was measured via a congestion score performed by a trained cardiologist. The score was on a scale from 0 to 10, split between severity of edema, pleural effusion and ascites. Higher scores indicated higher severity. Successful decongestion was defined as a 0 without escalation of therapy. Secondary outcomes were the composite end point of all-cause mortality or rehospitalization within 3 months and the duration of hospital admission.

A total of 515 patients were induced in analysis. The primary outcome was achieved in 108 of 256 (42.2%) patients in the acetazolamide group compared with 79 of 259 (30.5%) patients in the placebo group (RR 1.46, 95% CI 1.17,1.82, *P* < *.001*). Composite all-cause mortality and rehospitalization for heart failure within 3 months was similar between groups (29.7% in acetazolamide group vs 27.8% in placebo, HR 1.07; 95% CI 0.78, 1.48). Mean duration of hospitalization was 8.8 days (95% CI 8.0, 9.5) for acetazolamide compared with 9.9 (9.5% CI 9.1, 10.8) for placebo with a treatment effect of 0.89 (95% CI 0.81,0.98). Safety and adverse effects were similar across the 2 trial groups with no cases of severe metabolic acidosis.

What is New – Evidence of Benefit for Adjunctive Therapy in Acute Decompensated Heart Failure

This RCT showed evidence to support the addition of IV acetazolamide vs placebo to standard IV loop diuretic therapy during hospitalization for acute decompensated heart failure in achieving successful decongestion.

Caveats – Common Medications and Patients with New Diagnoses or Lower Maintenance Doses Excluded

Patients were already on oral maintenance loop diuretics before study enrollment and therefore, study results are not generalizable to patients with new diagnoses or with maintenance doses lower than 40 mg of furosemide. Patients on diuretic medications that acted on the proximal tubule were also excluded, and this includes those on SGLT2 inhibitors which may represent an increasing number of heart failure patients. Finally, this study recruited exclusively in Belgium, which has a different health care system than the US.

Challenges to Implementation

Acetazolamide may cause hypotension and may also change in efficacy based on renal status. Neurohumoral blockers were kept constant during the study and titration of patient's maintenance cardiac medications may adjust the adverse effect profile. This may not be possible when the acute decompensated heart failure is in the context of comorbidities. Caution should be used with blood pressure as well as maintenance medication doses while using IV acetazolamide as treatment. In addition, the effects of acetazolamide are unknown in patients also using SGLT-2 inhibitors.

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