EDITORIAL

Oral acetazolamide: a possible strategy to relieve congestion in worsening heart failure?

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Acute heart failure (AHF) represents a potentially life-threatening condition necessitating immediate evaluation, followed by prompt initiation or intensification of treatment.[1,2] Decongestion-focused treatments are pivotal in the management of AHF.[3] While loop diuretics continue to serve as the primary approach for managing AHF in hospitalized patients, the number of evidence-based decongestion strategies is limited.[4,5]

There has been a growing interest in combining acetazolamide with standard intravenous loop diuretics in decongestive therapy for AHF patients. Acetazolamide inhibits carbonic anhydrase in the proximal renal tubule, resulting in increased diuresis and natriuresis.[6,7] The notion is that the combination of distinct classess of diuretics may act through different mechanisms in different parts of the nephron, counteracting the diuretic resistance.[7] The goal behind this strategy is to enhance the overall effectiveness and efficiency of treatment. A pilot DIURESIS-CHF trial[8] previously examined the impact of intravenous acetazolamide, administered at doses ranging from 250 to 500 mg plus bumetanide 1–2 mg twice daily vs high-dose loop diuretics (bumetanide twice a day, with a daily dose twice the oral maintenance dose) on boosting the natriuretic response and enhancing the efficacy of loop diuretics in patients with AHF. More recently, the ADVOR (Acetazolamide in Acute Decompensated Heart Failure with Volume Overload) trial[9] demonstrated that, in patients hospitalized for AHF, intravenous administration of acetazolamide 500 mg daily for 3 days in addition to a standard loop diuretic resulted in a greater incidence of successful decongestion, as compared with a loop diuretic alone. However, the lack of impact on clinical outcomes precluded any recommendation in the 2023 European Society of Cardiology guideline update on the management of HF.[10]

Oral administration of diuretics often results in their restricted and inconsistent bioavailability. Indeed, the presence of intestinal mucosal edema and reduced blood flow in the gastrointestinal tract limit absorption, potentially leading to increased resistance to diuretics in AHF. It is uncertain whether absorption of oral acetazolamide is disturbed or whether it retains comparable effectiveness in decongestion, as compared with its intravenous formulation.

In this issue of *Polish Archives of Internal Medicine*, Kosiorek et al[11] try to fill this knowledge gap. In this prospective, randomized, single-center study conducted between February 2020 and November 2021, 61 hospitalized patients with AHF were randomly assigned to receive either standard of care or 250 mg of oral acetazolamide daily for 2 days in addition to a standard diuretic therapy. The group receiving acetazolamide, as compared with the control group, showed higher cumulative diuresis after 48 and 72 hours as well as greater negative fluid balance, weight loss at 48 hours, and weight reduction throughout the hospital stay, increased natriuresis, and elevated serum chloride concentrations.

Interestingly, despite the suspected constraints in bioavailability caused by intestinal mucosal edema in AHF patients, the study demonstrated effective diuresis through the combination therapy employing oral acetazolamide. This point should be further investigated in pharmacokinetic studies.

Notably, there were no elevations in creatinine concentration or the levels of urinary renal biomarkers (ie, neutrophil gelatinase-associated lipocalin, kidney injury molecule-1, and cystatin C), indicating a favorable renal safety profile.[11] Taken together, these findings support the utilization of a small dosage of oral acetazolamide for achieving a more effective decongestion in patients with AHF. Of note, in a secondary analysis of the ADVOR trial,[12] the use of acetazolamide was accompanied by a 3-fold increase in the risk of worsening renal function. Thus, further data

are needed to support the addition of acetazolamide to a standard diuretic regimen to aid decongestion,[10,12] also considering the limitations of this hypothesis-generating study, which included a small sample size and lacked assessment of longitudinal changes in N-terminal pro–B-type natriuretic peptide levels and effective decongestion at discharge. Additional studies are also warranted to assess the impact of adding acetazolamide on the possibility to discharge patients on all the 4 pillars of HF therapy, and possibly also evaluate the rates of HF decompensation during the first month after discharge.[13]

As highlighted by the authors,[11] a small number of patients were using sodium glucose cotransporter 2 (SGLT-2) inhibitors. In the ADVOR trial,[9] the patients on SGLT-2 inhibitors were excluded. Given also the results of trials investigating the role of SGLT-2 inhibitors in patients with AHF, further research is essential to ascertain the safety and efficacy of combining these 2 classes of diuretics—SGLT-2 inhibitors and acetazolamide.[14,15]

Despite these possible drawbacks, the study by Kosiorek et al[11] presents encouraging findings concerning the diuretic, natriuretic, and chloride reabsorption effects of a combined decongestive approach based on utilizing oral acetazolamide in patients with AHF who experience volume overload. The advantages of oral drug administration are widely recognized, involving improved patient adherence, lower risk of infection, avoidance of discomfort, and cost-effectiveness. Furthermore, the oral form may be a valuable option in patients experiencing an episode of HF worsening in the outpatient setting; thus, the current study potentially extends its application to outpatient individuals with early-stage AHF. Adequately powered clinical trials are needed to clarify the effect of oral acetazolamide on surrogate end points (eg, decongestion at discharge, as in ADVOR[9]) and clinical outcomes in AHF.[10]

ARTICLE INFORMATION

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