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ACETAZOLAMIDE AS ADDITIONAL THERAPY IN PATIENTS WITH DECOMPENSATED HEART FAILURE

Ahmed Elsayed Ahmed[1], Fatema Sayed Helal Salman[2]*, Ghadeer Ahmed Alhawsawi[3], Hussain Said Alslatin[4], Mohammed Ali Alqarni[4], Kholoud Qassim Alhafaf[5], Mohammad Fahmy Flimban[6], Mohammed Ahmed Alzahrani[7], Rahmah Naif Alzaid[8], Reeman Mohammed Aljohani[9], Wafa Mohammed Almuallim[10], Yasmin Salem Almesad[11]

1. *Faculty of Medicine, Al Mouwasat Hospital, Al Khobar, Saudi Arabia.*
2. *Faculty of Medicine, Zhejiang University, Zhejiang, China.*
3. *Faculty of Medicine, Taif University, Taif, Saudi Arabia.*
4. *Faculty of Medicine, King Khalid University, Abha, Saudi Arabia.*
5. *Physiotherapist, King Fahd Hospital, Jazan, Saudi Aarbia.*
6. *Faculty of Medicine, King Abdulaziz University Hospital, Jeddah, Saudi Arabia.*
7. *Faculty of Medicine, King Saud Bin Abdulaziz University, Riyadh, Saudi Arabia.*
8. *Faculty of Pharmacy, Aldawaa Pharmacies, AlJawf, Saudi Arabia.*
9. *Faculty of Medicine, Taibah University, AlMadinah AlMonawarah, Saudi Arabia.*
10. *Faculty of Medicine, Al-Rayan Colleges, AlMadinah AlMonawarah, Saudi Arabia.*
11. *Faculty of Medicine, Jaber AlAhmad AlSabah Hospital, Kuwait, Kuwait.*

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ABSTRACT

A functional limitation and the need for prompt intervention come from the heart's inability to eject or accommodate blood within acceptable physiological pressure ranges, known as decompensated heart failure (DHF). It has undeniable epidemiological significance and clinical features. In AHF patients at high risk of diuretic resistance, the administration of acetazolamide enhances the natriuretic response to loop diuretics compared to an increase in loop diuretic dose. Decompensated heart failure (DHF) is a clinical syndrome characterized by the heart's not being able to eject and/or accommodate blood within accepted physiological pressure parameters, resulting in a functional limitation and the need for immediate intervention. It has undeniable epidemiological significance, as well as clinical features that have a direct impact on treatment. In AHF patients at high risk of diuretic resistance, the administration of acetazolamide enhances the natriuretic response to loop diuretics compared to an increase in loop diuretic dose. Acetazolamide improves diuretic efficacy, especially in cases of diuretic resistance. However, the balance between the possible advantages and risks must be carefully considered. The decision to include acetazolamide in the treatment plan should be guided by individual patient features such as renal function and comorbidities. The Medline, Pubmed, Embase, NCBI, and Cochrane databases were searched. Incidence, etiology, and management options were analyzed. Acetazolamide improves diuretic efficacy, especially in cases of diuretic resistance. However, the balance between the possible advantages and risks must be carefully considered. The decision to include acetazolamide in the treatment plan should be guided by individual patient features such as renal function and comorbidities.

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Introduction

Heart failure strikes 1 to 2% of the global population. There is a greater incidence of these occurring in industrialized countries, but its toll has expanded globally and it is linked to a higher probability of death and hospitalization. Decompensated heart failure, or DHF, is a medical condition in which the heart's structural or functional change causes it to be unable to eject and/or

Corresponding Author: Fatema Sayed Helal Salman; Faculty of Medicine, Zhejiang University, Zhejiang, China. E-mail: Fatima1496@outlook.com.

accommodate blood within acceptable physiological pressure parameters, resulting in a functional limitation and requiring immediate medical treatment [1]. It has undeniable epidemiological significance, as well as clinical features that have a direct impact on treatment. Diuretics are commonly used to treat retention of fluid in heart failure, however, there is little evidence pointing to this treatment reducing the mortality rate. The European Society of Cardiology (ESC) still recommends using diuretics to establish appropriate fluid balance in patients with chronic or acute overhydration symptoms [2].

Every year, many people are released from the hospital with residual signs of fluid buildup despite the use of high-dose loop diuretics, which is a strong indicator of adverse outcomes. Also, the Diuretic Optimization Strategies Evaluation (DOSE) trial found that after 72 hours of treatment, patients no longer showing any symptoms of clinical congestion added up to 15% only [3]. Additionally, 20% of patients were discharged from the hospital with a greater weight than when they arrived, according to the Acute Decompensated Heart Failure National Registry (ADHERE). Even though sequential diuretic therapy has been demonstrated to be a more effective decongestive approach than loop diuretics alone, there is a dearth of information regarding the most effective diuretic agent, routes of administration, and administration schedules [4].

Acetazolamide reduces carbonic anhydrase and minimizes salt absorption in the proximal tubule. Since it was shown to be more useful and less toxic than sulfanilamide diuretics, it was first used as a diuretic to manage congestive heart failure. Its beneficial decongestive qualities were showcased through many case studies about the treatment of acetazolamide on heart failure patients in the 1950s. However, acetazolamide use has been declining even though loop diuretics are typically thought to be more effective [5]. According to recent studies, a compensatory increase in distal tubular Na-Cl co-transporter activity brought on by a drop in pendrin expression may be the origin of the acetazolamide ceiling effect. Thus, combining thiazide diuretics with acetazolamide is a viable diuretic-resistant therapeutic option according to this finding.

Acetazolamide is thought to improve decongestion by reducing proximal tubular reabsorption of salt and to enhance diuretic efficiency when used together with diuretics [6], but human trials on the topic of the efficacy of acetazolamide to treat fluid overload in heart failure patients are few and far between.

Materials and Methods

PubMed database was used for articles selection, and the following keys were used in the mesh ((" Acetazolamide " [Mesh]) AND (" decompensated heart failure " [Mesh]) OR ("Management" [Mesh])). In regards to the inclusion criteria, the articles were selected based on the inclusion of one of the following topics: Acetazolamide as additional therapy in patients with decompensated heart failure.

Acetazolamide as additional therapy in patients with decompensated heart failure features and management. Exclusion criteria were all other articles, which did not have one of these topics as their primary endpoint. Around 90 publications were chosen as the most clinically relevant out of 1,202 articles indexed in the previous two decades, and their full texts were evaluated. A total of 31 of the 90 were included after a thorough examination. Additional research and publications were found using reference lists from the recognized and linked studies. Expert consensus recommendations and commentary were added where relevant to help practicing physicians assess Acetazolamide as additional therapy in patients with decompensated heart failure in the simplest and most practical way possible.

Results and Discussion

Globally, CHF and acute decompensated heart failure are among the most common conditions warranting admission to hospitals in developed countries. The number of cases of heart failure is high: heart failure is estimated to be suffered by 1-2% of the population in affluent countries, with this percentage rising to 10% in people aged 70 and up. Ten million people in Europe are thought to have heart failure with concurrent ventricular dysfunction and an additional ten million have heart failure with intact ejection fraction(HFPEF) [7]. According to data from 2012, 21.5% of 1,137,572 hospitalizations for circulatory system disorders in Brazil were for heart failure, with 70% of patients being over the age of 60 and the death rate in-hospital for said condition at around 9.5% [8]. Hospitalization costs for decompensation account for roughly 60% of overall HF treatment costs [9]. Of all patients discharged, readmission is around 25% while the mortality rate sits at approximately 10% within 90 days of treatment [9]. The most common cause of heart failure is ischemic cardiomyopathy [10], but valvular, hypertensive, and chagasic cardiomyopathies are also common in Brazil.

One of the most significant early therapy aims in patients with acute decompensated heart failure is decongestion via increased diuresis. Loop diuretics, along with other pharmacotherapeutic approaches for boosting urine production, constitute the foundation of diuretic therapy. This includes both loop diuretics and other medications such as acetazolamide (a carbonic anhydrase inhibitor that functions in the kidney's proximal tubule) and HCTZ (a competitor for the sodium-chloride cotransporter in the distal convoluted tubule, resulting in increased natriuresis and output of urine). No advances in terms of novel treatments for acute decompensated heart failure have been made in decades, and there is a crucial unmet need in that attempts at new medications have not demonstrated any benefit to individuals suffering from acute decompensated heart failure on post-discharge outcomes, according to study trials [11].

In addition to typical diuretic treatments, providing vasopressin antagonism, natriuretic peptides (nesiritide or ularitide) [12], and ultrafiltration [8, 9] to individuals with acute decompensated heart failure have not demonstrated consistent therapeutic advantages. However, the recent ADVOR (Acetazolamide in Decompensated Heart Failure with Volume Overload) trial’s

objective was to improve diuresis in contrast to placebo by utilizing loop diuretics together with acetazolamide (500 mg once a day) [13]. It comprised patients with acute decompensated heart failure who were randomly selected to receive an intravenous bolus of acetazolamide or routine diuretic treatment for three days during the acute in-hospital phase.

The acetazolamide group had more successful decongestion, at 42.2%, than the placebo group (30.5%), spent less time in the hospital, and showcased improved natriuresis and diuresis without changes in important clinical outcomes such as WRF, hypotension, and hypokalaemia. Absolute diuretic effects were clinically insignificant, with an increase of only 0.5 L in the acetazolamide group compared to placebo 48 hours after randomization (Day 3 of the study procedure). However, it is debatable if these changes warrant a modification to clinical treatment strategies despite these results being statistically significant. During the follow-up at three months, no significant differences were found in all-cause mortality or rehospitalization for heart failure [29.7% vs. 27.8%; with death from any cause]. [Acetazolamide (39.2%) vs. placebo (31.0%)] with an increase in the frequency of renal safety endpoint events in the acetazolamide group [13].

Due to its ability to effectively relieve congestion, American and European organizations recommend acetazolamide for the diagnosis and treatment of heart failure in class I recommendations. The benefits of acetazolamide in this population are significant given that congestion is linked to bad prognosis in individuals afflicted with heart failure. The medication's immediate and sustained surge in urine and sodium excretion is likely responsible for the higher decongestion rates observed with acetazolamide. These findings stress the importance of tackling congestion quickly and forcefully, and they encourage employing natriuresis to assess the efficacy of diuretic medication [14].

Given the pathophysiology involved, there are many reasons to treat heart failure with acetazolamide in addition to loop diuretic therapy. The natriuretic action of loop diuretics is first amplified by acetazolamide, which increases the amount of salt that reaches Henle's loop. This indicates that loop diuretics are successful in acetazolamide-treated persons, as seen by increased natriuresis and diuresis. It is crucial to highlight that the efficiency of loop diuretics has been demonstrated to be a reliable and distinct indicator of clinical outcomes in acute heart failure, albeit whether this association is causative has yet to be determined [15]. Also, inhibiting proximal salt reabsorption increases sodium and chloride supply to macula densa cells at the end of the Henle loop, activating tubuloglomerular feedback in the same way that sodium-glucose co-transporter 2 (SGLT2) inhibitors do [16]. Finally, it is speculated that acetazolamide has innate kidney-protecting properties and has been proven in animal studies to reduce ischemia-reperfusion injury, perhaps by increasing vasodilation via nitric oxide stimulation [17]. Furthermore, some trials prior to the present age of heart failure treatments with neurohumoral blockers used acetazolamide as an effective drug to beat resistance to loop diuretics [18].

Conclusion

Acetazolamide's significance as an adjunct therapy for individuals suffering from decompensated heart failure is a complex component of cardiovascular treatment. While the possible advantages of acetazolamide, a carbonic anhydrase inhibitor, in increasing diuresis and reducing fluid overload have been investigated, its use in the setting of heart failure requires careful evaluation.

Current study evidence suggests that in cases of diuretic resistance, acetazolamide may help diuretics work better. However, in the clinical situation, the equilibrium between potential advantages and risks, such as electrolyte imbalances and metabolic acidosis, must be carefully assessed. Individual patient characteristics such as kidney health and comorbidities should guide the choice to incorporate acetazolamide in the treatment plan. However, further research on acetazolamide use in decompensated heart failure is required to establish the most effective dosage, timing, and patient selection standards. Improving recommendations for treatment and patient care will require a thorough study of the impact of acetazolamide on hemodynamics, renal function, and overall medical outcomes.

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References

1. Bocchi EA, Vilas-Boas F, Perrone S, Caamaño AG, Clausell N, Moreira MD, et al. I Latin American guidelines for the assessment and management of decompensated heart failure. Arq Bras Cardiol. 2005;85 Suppl 3:1-48.
2. Kelder JC, Cramer MJ, van Wijngaarden J, van Tooren R, Mosterd A, Moons KG, et al. The diagnostic value of physical examination and additional testing in primary care patients with suspected heart failure. Circulation. 2011;124(25):2865-73.
3. Felker GM, Lee KL, Bull DA, Redfield MM, Stevenson LW, Goldsmith SR, et al. Diuretic strategies in patients with acute decompensated heart failure. N Engl J Med. 2011;364(9):797-805.

4. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) With the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2021;42(36):3599-726.
5. Zahedi K, Barone S, Xu J, Soleimani M. Potentiation of the effect of thiazide derivatives by carbonic anhydrase inhibitors: molecular mechanisms and potential clinical implications. PloS one. 2013;8(11):e79327.
6. Mullens W, Dauw J, Martens P, Verbrugge FH, Nijst P, Meekers E, et al. Acetazolamide in acute decompensated heart failure with volume overload. N Engl J Med. 2022;387(13):1185-95.
7. Hunt SA, Abraham WT, Chin MH, Feldman AM, Francis GS, Ganiats TG, et al. Focused update incorporated into the ACC/AHA 2005 Guidelines for the Diagnosis and Management of Heart Failure in Adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: developed in collaboration with the International Society or Heart and Lung Transplantation. Circulation. 2009;119(14):e391-479.
8. Brasil MDS. Datasus: morbidade hospitalar do SUS por local de internação – Brasil [Internet]. Brasília (DF):Ministério da Saúde; c2008. [citado 2013 Set 18]. Disponível em
9. Gheorghiade M, Zannad F, Sopko G, Klein L, Piña IL, Konstam MA, et al. Acute heart failure syndromes. Circulation. 2005;112(25):3958-68.
10. Adams Jr KF, Fonarow GC, Emerman CL, LeJemtel TH, Costanzo MR, Abraham WT, et al. Characteristics and outcomes of patients hospitalized for heart failure in the United States: rationale, design, and preliminary observations from the first 100,000 cases in the Acute Decompensated Heart Failure National Registry (ADHERE). Am Heart J. 2005;149(2):209-16.
11. Packer M, O'Connor C, McMurray JJ, Wittes J, Abraham WT, Anker SD, et al. Effect of ularitide on cardiovascular mortality in acute heart failure. N Engl J Med. 2017;376(20):1956-64.
12. O'Connor CM, Starling RC, Hernandez AF, Armstrong PW, Dickstein K, Hasselblad V, et al. Effect of nesiritide in patients with acute decompensated heart failure. N Engl J Med. 2011;365(1):32-43.
13. Mullens W, Dauw J, Martens P, Verbrugge FH, Nijst P, Meekers E, et al. Acetazolamide in acute decompensated heart failure with volume overload. N Engl J Med. 2022;387(13):1185-95.
14. Mullens W, Dauw J, Martens P, Verbrugge FH, Nijst P, Meekers E, et al. Acetazolamide in acute decompensated heart failure with volume overload. N Engl J Med. 2022;387(13):1185-95.
15. H. Verbrugge F, Dupont M, B. Bertrand P, Nijst P, Penders J, Dens J, et al. Determinants and impact of the natriuretic response to diuretic therapy in heart failure with reduced ejection fraction and volume overload. Acta Cardiol. 2015;70(3):265-73.
16. Verbrugge FH, Martens P, Mullens W. SGLT-2 inhibitors in heart failure: implications for the kidneys. Curr Heart Fail Rep. 2017;14:331-7.
17. An Y, Zhang JZ, Han J, Yang HP, Tie L, Yang XY, et al. Hypoxia-inducible factor-1α dependent pathways mediate the renoprotective role of acetazolamide against renal ischemia-reperfusion injury. Cell Physiol Biochem. 2013;32(5):1151-66.
18. Knauf H, Mutschler E. Sequential nephron blockade breaks resistance to diuretics in edematous states. J Cardiovasc Pharmacol. 1997;29(3):367-72.