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EC PHARMACOLOGY AND TOXICOLOGY

Research Article

Acetazolamide Versus Thiazides with Loop Diuretics in Acute Decompensated Heart Failure

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Received: November 07, 2024; **Published:** November 26, 2024

Abstract

Introduction: Acetazolamide is a carbonic anhydrase inhibitor that reduces sodium reabsorption in the renal proximal tubule. It has demonstrated benefit in reducing volume overload in combination with loop diuretics compared to loop monotherapy in acute decompensated heart failure (ADHF) [1]. However, its efficacy and safety compared to the combination of thiazide and loops is unclear.

Objective: To determine whether acetazolamide and loop is superior to thiazide and loop or all three diuretic classes combined in ADHF.

Methods: Retrospective, single-centered, cohort study. Collected data for patients who received intravenous chlorothiazide, oral metolazone, or intravenous acetazolamide from 2021 to 2023. Inclusion criteria was patients aged 18 years or older with ADHF on either loop and thiazide concomitantly or loop and acetazolamide concomitantly. Exclusion criteria was acetazolamide maintenance therapy or extracorporeal membrane oxygenation during hospitalization.

Results: Total 340 patients divided into thiazide and loop (group 1, n = 144), acetazolamide and loop (group 2, n = 105), and all three classes of diuretics (group 3, n = 91). The primary outcome of average net daily urine output was non-significant across all groups before and after adjusting for confounders, including weight, inotrope use, and left ventricular ejection fraction (-1305.0 mL/day vs -1240.0 mL/day vs -1640.0 mL/day, p = 0.223 before adjustment, p = 0.790 and p = 0.321 for group 1 vs 3 and group 2 vs 3 respectively after adjustment). The secondary outcomes, including length of hospital stay, 30-day and 90-day rehospitalization and mortality, and inpatient mortality, were also non-significant.

Conclusion: There is no significant difference in average daily net urine output or safety outcomes among patients treated for ADHF with thiazide and loop, acetazolamide and loop, or all three diuretic classes, even after adjusting for confounders. Further studies are warranted to determine optimal timing and target doses of each diuretic when used in combination.

Keywords: *Cardiology; Heart Failure; Diuretics; Acetazolamide; Acute Decompensated Heart Failure*

Abbreviation

ADHF: Acute Decompensated Heart Failure

Introduction and Background

Current guidelines recommend IV loop diuretics to reduce the symptoms of fluid overload in patients with acute decompensated heart failure (ADHF). In the setting of diuretic resistance, thiazide diuretics may also be used in combination with loop diuretics to increase diuresis. Acetazolamide is a carbonic anhydrase inhibitor that reduces NHE3-mediated (natrium-hydrogen exchanger 3) sodium absorption on the proximal tubule of the kidney. While acetazolamide alone exhibits weak diuretic effects, its combination with loop diuretics may enhance diuresis. The ADVOR 2022 trial studied the impact of IV acetazolamide plus loop versus loop diuretic alone in patients with ADHF, demonstrating that the addition of acetazolamide resulted in a greater incidence of successful decongestion within three days and shorter hospital stays compared to loop diuretic alone [1,2]. This study aims to evaluate the effectiveness of thiazide plus IV loop diuretic, IV acetazolamide plus IV loop diuretic, and the combination of all three diuretic classes in reducing volume overload in patients with ADHF.

Purpose of the Study

To determine whether acetazolamide and loop is superior to thiazide and loop or all three diuretic classes combined in ADHF.

Significance

There may be minimal or no clinical benefit in adding acetazolamide for diuresis with regards to volume reduction; however, acetazolamide may be preferred in select patients, such as those with elevated serum bicarbonate levels or for renal protection in patients expected to be on longer durations of diuretic therapy.

Materials and Methods

Trial design and oversight: This single-centered, retrospective cohort study was conducted using the EPIC electronic health record at Loma Linda University Medical Center for patients admitted between September 1, 2021 and August 1, 2023 who received IV chlorothiazide, PO metolazone, or IV acetazolamide. Patients' information and clinical data were recorded using the RedCap secure web application, and codes were created for re-identification purposes. The protocol was approved by our institutional IRB.

Patients: Patients aged at least 18 years or older with acute decompensated heart failure as indicated by history and physical examination or progress notes, and at least one clinical sign of fluid overload (edema, pulmonary congestion, shortness of breath, or ascites) were included if they received thiazide and IV loop diuretics concomitantly or IV acetazolamide and IV loop diuretics concomitantly. Patients were excluded if they were on acetazolamide maintenance therapy, extracorporeal membrane oxygenation (ECMO) anytime during the hospital stay, or if there were missing urine output records for any days while on diuretic therapy.

Endpoints: The primary outcome was average net urine output on days of diuretic therapy. Secondary outcomes included length of hospital stay, 30-day and 90-day rehospitalization, 30-day and 90-day mortality, and inpatient mortality. Safety outcomes included incidence of hypokalemia (serum potassium less than 3.5 mEq/L), an increase in serum creatinine greater than or equal to 1.5 times baseline, and incidence of arrhythmias while on diuretic therapy.

Statistical analysis: Descriptive statistics were measured for each treatment group and included as median with minimum and maximum, mean with standard deviation, or as percentages as appropriate. P-values for baseline characteristics were calculated using Chi-squared test, Kruskal-Wallis test, or ANOVA, depending on the number and type of variables, as well as the distribution of the data. The primary outcome of average net urine output per day was analyzed with Kruskal-Wallis test and was adjusted for possible confounders using a multiple linear regression. Secondary outcomes were presented as percentages and evaluated using Chi-square test to assess for the association of these variables among the three treatment groups. Data analysis was performed at an alpha of 0.05 using SPSS 29.0.

Results and Discussion

Patients: Between September 1, 2021 and August 1, 2023, a total of 792 patients were screened, of whom 377 did not meet inclusion criteria and 75 met exclusion criteria. Of the remaining patients, 144 were included in group 1 (thiazide and loop); 105 were included in group 2 (acetazolamide and loop); and 91 were included in group 3 (thiazide, acetazolamide, and loop). The characteristics of the patients at baseline were well balanced between the groups (Table 1). Median age was approximately 63 years, and the median BMI was approximately 30 kg/m^2 across all groups. The only statistically significant differences in baseline characteristics were left ventricular ejection fraction (LVEF) and maintenance loop diuretics use prior to admission, with groups 1 and 3 having more patients with LVEF < 40% and more than 50% of patients on maintenance loop diuretics. Total doses of diuretics are also reported in table 2.

		Thiazide + Loop (N = 144)	Acetazolamide + Loop (N = 105)	All 3 classes of diuretics (N = 91)	P-value
Age, mean (SD), y		63.3 (16.3)	62.8 (15.2)	62.4 (16.2)	0.912[b]
BMI, median (min-max), kg/m^2		30.2 (16.6-86.8)	29.3 (14-91.1)	30.4 (16.6-73.5)	0.858[a]
Weight, median (min-max), kg		87 (36-267)	88 (24-337)	95 (44-245)	0.078[a]
Sex, No. (%)	Male	93 (64.6)	59 (56.2)	57 (62.6)	0.391
	Female	51 (35.4)	46 (43.8)	34 (37.4)	
Race, No. (%)	White	60 (41.7)	61 (58.1)	43 (47.3)	0.047*
	Black or African American	25 (17.4)	16 (15.2)	14 (15.4)	
	Asian	7 (4.9)	1 (1.0)	3 (3.3)	
	Hispanic	52 (36.1)	25 (23.8)	27 (29.7)	
LVEF, mean (SD), %	<20	45 (33.6)	16 (16.8)	29 (34.5)	0.037*
	20-40	30 (22.4)	22 (23.2)	16 (19.0)	
	>40	59 (44.0)	57 (60.0)	39 (46.4)	
NYHA Class, No. (%)	Class I	0 (0.0)	1 (2.1)	0 (0.0)	0.184
	Class II	6 (7.0)	1 (2.1)	6 (8.6)	
	Class III	56 (65.1)	33 (70.2)	37 (52.9)	
	Class IV	24 (27.9)	12 (25.5)	27 (38.6)	
All 4 GDMT classes prior to admission, No. (%)		2 (1.4)	3 (2.9)	5 (5.5)	0.192
Oral loop diuretics prior to admission, No. (%)		96 (66.7)	49 (46.7)	52 (57.1)	0.007*
Smoking, No. (%)	No	82 (56.9)	53 (50.5)	48 (52.7)	0.583
	Yes	62 (43.1)	52 (49.5)	43 (47.3)	
Alcohol use, No. (%)	No	100 (69.4)	77 (73.3)	60 (65.9)	0.529
	Yes	44 (30.6)	28 (26.7)	31 (34.1)	
Substance abuse, No. (%)	No	99 (68.8)	76 (72.4)	65 (71.4)	0.807
	Yes	45 (31.3)	29 (27.6)	26 (28.6)	
All values represent numbers with percentage except where indicated with mean and standard deviation or median with minimum and maximum.					
All p-values indicate Chi-square except where indicated with [a] for Kruskal-Wallis test and [b] for ANOVA. Quality of evidence: Rating 3. *Indicates significance at an alpha of 0.05.					

Table 1: *Baseline characteristics.*

	Thiazide + Loop (N = 144)	Acetazolamide + Loop (N = 105)	All 3 classes of diuretics (N = 91)
Metolazone, median (min-max), mg	12.5 (2.5-90)	---	15 (2.5-1000)
Chlorothiazide, median (min-max), mg	500 (200-2500)	---	1000 (500-9500)
Acetazolamide, median (min-max), mg	---	500 (250-7250)	1000 (250-7000)
All values represent median (min-max). Quality of evidence: Rating 3.			

Table 2: *Total average doses of diuretics.*

Primary outcome: The primary outcome of average net urine output on days of diuretic therapy was -1305.0 mL/day (-6645-1762) in group 1, -1240.0 mL/day (-6645-1762) in group 2, and -1640.0 mL/day (-4283-670) in group 3 (p = 0.223) (Table 3). The primary outcome did not reach statistical significance between group 1 versus group 3 and group 2 versus group 3 after adjusting for possible confounders, including baseline weight, serum creatinine, inotrope and vasopressor use, baseline left ventricular ejection fraction, and baseline guideline-directed medication therapies and oral loop diuretics (p = 0.790 and p = 0.321, respectively) (Table 4).

		Thiazide + Loop (N = 144)	Acetazolamide + Loop (N = 105)	All 3 classes of diuretics (N = 91)	P-value
Urine Output, median (min-max), mL/day		-1305.0 (-6645-1762)	-1240.0 (-7128-328)	-1640.0 (-4283-670)	0.223[a]
Scr, No. (%), mg/dL	1.5x Baseline	26 (18.1)	12 (11.4)	21 (23.1)	0.095
CO_2, No. (%), mmol/L	>30	45 (31.3)	53 (50.5)	59 (64.8)	<0.001*
K, No. (%), mEq/L	<3.5	66 (45.8)	51 (48.6)	63 (69.2)	0.001*
K Replacement, mEq/d		86	69	75	0.333
Arrhythmias, No. (%)	Total	38 (26.4)	25 (24.0)	31 (34.1)	0.265
	Ventricular tachycardia	1 (2.6)	3 (12.0)	7 (22.6)	0.055
	Atrial fibrillation/ flutter	33 (86.8)	20 (80.0)	22 (71.0)	
	Supraventricular tachycardia	0 (0.0)	1 (4.0)	2 (6.5)	
	Other	4 (10.5)	1 (4.0)	0 (0.0)	
Inotrope, No. (%)		36 (25.0)	6 (5.7)	38 (41.8)	<0.001*
Vasopressor, No. (%)		20 (14.0)	8 (7.6)	27 (30.0)	<0.001*
All values represent numbers with percentage except where indicated with median with minimum and maximum. *Indicates significance at an alpha of 0.05. All p-values indicate Chi-square except where indicated with [a] for Kruskal-Wallis test. Quality of evidence: Rating 3.					

Table 3: *Primary outcome and safety outcomes.*

	B	Std. Error	P-value	95% CI	
Thiazide + Loop vs. All 3 classes of diuretics	-42.3	159.0	0.790	-355.2	270.6
Acetazolamide + Loop vs. All 3 classes of diuretics	-181.4	182.6	0.321	-540.7	178.0
Weight at baseline	-4.7	1.6	0.003	-7.8	-1.6
Serum creatinine	-52.8	172.3	0.759	-392.0	286.3
Inotrope	-91.3	177.2	0.607	-440.0	257.4
Vasopressor	-335.7	188.7	0.076	-707.1	35.6
LVEF at admission	343.5	80.1	0.000	185.7	501.2
All 4 GDMT classes prior to admission	122.4	411.7	0.766	-687.8	932.7
Oral loop diuretics prior to admission	-35.6	132.7	0.789	-296.8	225.7
Dependent Variable: Urine output. Quality of evidence: Rating 3.					

Table 4: *Multiple linear regression for the effect of diuretics on urine output.*

Secondary outcomes: The secondary outcomes of length of hospital stay, 30-day and 90-day rehospitalization, 30-day and 90-day mortality, and inpatient mortality did not show statistically significant differences among the three groups (Table 5). 30-day rehospitalization occurred in 33 patients (22.9%) in group 1, 26 patients (24.8%) in group 2, and 22 patients (24.4%) in group 3 (p = 0.941). 30-day mortality occurred in 5 patients (3.5%) in group 1, 4 patients (3.8%) in group 2, and 2 patients (2.2%) in group 3 (p = 0.799). 90-day rehospitalization and mortality is presented in table 5. Inpatient mortality occurred in 16 patients (11.1%) in group 1, 12 patients (11.4%) in group 2, and 12 patients (13.2%) in group 3 (p = 0.883). Of note, congestive heart failure (CHF) was the cause of 30-day and 90-day rehospitalization for 42.4%, 35.7%, and 50% of patients in groups 1, 2, and 3, respectively, and 40%, 50%, and 30.4% of patients in groups 1, 2, and 3 respectively. The median length of stay was 7 days (min-max: 1-64) for group 1, 7 days (min-max: 1-74) for group 2, and 12 days (min-max: 2-113) for group 3.

		Thiazide + Loop (N = 144)	Acetazolamide + Loop (N = 105)	All 3 classes of diuretics (N = 91)	P-value
30-Day Rehospitalization, No. (%)		33 (22.9)	26 (24.8)	22 (24.2)	0.941
Cause, No. (%)	CHF	14 (42.4)	10 (35.7)	11 (50.0)	0.449
	Arrythmia	1 (3.0)	1 (3.6)	2 (9.1)	
	MI	2 (6.1)	0 (0.0)	0 (0.0)	
	Stroke	0 (0.0)	0 (0.0)	0 (0.0)	
	Other	16 (48.5)	17 (60.7)	9 (40.9)	
90-Day Rehospitalization, No. (%)	Total	36 (25.0)	22 (21.0)	23 (25.3)	0.707
Cause	CHF	14 (40.0)	11 (50.0)	7 (30.4)	0.627
	Arrythmia	3 (8.6)	2 (9.1)	1 (4.3)	
	MI	1 (2.9)	1 (4.5)	0 (0.0)	
	Other	17 (48.6)	8 (36.4)	15 (65.2)	
30-Day Mortality, No. (%)		5 (3.5)	4 (3.8)	2 (2.2)	0.799
90-Day Mortality, No. (%)		2 (1.4)	5 (4.8)	3 (3.3)	0.290
Inpatient Mortality, No. (%)		16 (11.1)	12 (11.4)	12 (13.2)	0.883
Length of Stay, median (min-max), days		7 (1-64)	7 (1-74)	12 (2-113)	
All values represent numbers with percentage. All p-values indicate Chi-square. Quality of evidence: Rating 3.					

Table 5: *Secondary outcomes.*

Safety and adverse events: Acute kidney injury was defined as an increase in serum creatinine to at least 1.5 times baseline. This occurred in 26 patients (18.1%) in group 1, 12 patients (11.4%) in group 2, and 21 patients (23.1%) in group 3 (p = 0.095) (Table 3). Serum bicarbonate greater than 30 mmol/L was observed in 45 patients (31.3%) in group 1, 53 patients (50.5%) in group 2, and 59 patients (64.8%) in group 3 (p < b 0.001). Hypokalemia, defined as a serum potassium level of less than 3.5 mEq/L, occurred in 66 patients (45.8%) in group 1, 51 patients (48.6% in group 2, and 63 patients (69.2%) in Group 3 (p = 0.001). Although more patients in group 3 experienced hypokalemia while on diuretic therapy, there was no statistically significant difference in the amount of potassium supplementation that patients received (86 mEq/day in group 1, 69 mEq/day in group 2, and 75 mEq/day in group 3, p = 0.333). Arrythmias occurred in 38 patients (26.4%) in group 1, 25 patients (24%) in group 2, 31 patients (34.1%) in group 3 (p = 0.265). The most common arrhythmia was atrial fibrillation or atrial flutter, occurring in 33 patients (86.8%) in group 1, 20 patients (80%) in group 2, and 22 patients (71%) in group 3. Significantly more patients in groups 1 and 3 received inotropes and vasopressors while on diuretic therapy compared to patients in group 2 (25% and 14% in group 1, 5.7% and 7.6% in group 2, and 41.8% and 30% in group 3) (p < 0.001 for both inotropes and vasopressors, respectively).

In this retrospective, single-centered study, there was no significant difference in average daily net urine output among patients who were treated with thiazide and loop diuretics, acetazolamide and loop diuretics, or all three classes of diuretics, even after adjusting for possible confounders. There was also no significant difference in hospital length of stay, 30-day and 90-day rehospitalization, 30-day and 90-day mortality, and inpatient mortality among the three groups.

Per the 2021 ESC guidelines on the management of acute decompensated heart failure, a satisfactory diuretic response can be defined as a urine sodium content greater than 50 - 70 mEq/L at 2 hours and/or a urine output greater than 100 - 150 mL/hour (2.4 - 3.6 L/day) during the first 6 hours [3]. Similarly, the 2022 Michigan Medicine Inpatient Diuretic Guideline for Patients with Acute Decompensated Heart Failure defines an adequate diuretic response as a urine output of at least 150 mL/hour (3.6 L/day) [4]. However, all three groups in this study demonstrated an average net urine output of less than 2 L/day. Although urine output may be influenced by various factors, such as baseline weight and volume status, none of the groups in this study reached the goal urine output defined by previous guidelines.

Of note, more patients in groups 1 and 3 required inotropes and vasopressors during their diuretic therapy, experienced an increase in serum creatinine more than 1.5 times baseline, and had lower left ventricular ejection fractions at baseline, compared to group 2. Additionally, significantly more patients in groups 1 and 3 were on maintenance oral loop diuretics prior to admission compared to patients in group 2. This suggests that patients in groups 1 and 3 may have had worse clinical status or further progression of heart failure compared to patients in group 2, which may affect the generalizability of the results.

Furthermore, significantly more patients in group 2 had serum bicarbonate levels greater than 30 mmol/L. This suggests that the population of patients who were initiated on acetazolamide combination therapy were those with elevated serum bicarbonate, which is consistent with acetazolamide's mechanism of action of excreting bicarbonate to increase urine output. If patients in the acetazolamide group had normal serum bicarbonate levels, the efficacy of acetazolamide and loop diuretic might have been less compared to thiazide and loop diuretic.

Limitation of the Study

There were several limitations to this study. First, as a retrospective chart review, the data was limited to what was recorded on the electronic health record. Second, the accuracy of urine output collection may have varied; however, patients with any missing urine output values on days of diuretic therapy were excluded from the study. Third, only rehospitalizations to Loma Linda University Medical Center were captured for the secondary outcomes. Fourth, home medications were collected from prior to admission medications lists, which may be unreliable. Lastly, data was not collected regarding the timing of when patients received each diuretic, and total doses of loop diuretics were not assessed.

Conclusion

In conclusion, there is no significant difference in average daily net urine output or safety outcomes among patients treated for acute decompensated heart failure with thiazide, acetazolamide, or all three classes of diuretics even after adjusting for potential confounders. Future studies are warranted to determine optimal timing and target doses of each diuretic when used in combination for acute decompensated heart failure.

Conflict of Interest and Funding Support

There are no financial interests or conflicts of interests to disclose.

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Volume 12 Issue 12 December 2024