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ORIGINAL ARTICLE

Acetazolamide as a potent chloride-regaining diuretic: short- and long-term effects, and its pharmacologic role under the 'chloride theory' for heart failure pathophysiology

Hajime Kataoka[1]

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Abstract
According to the "chloride theory" for heart failure (HF) pathophysiology, manipulation of the serum chloride concentration is an important therapeutic target. This study determined the short- and long-term effects of acetazolamide (Diamox), a potential chloride-regaining diuretic, on peripheral blood, serum electrolytes, and renal function. Effects of low-dose Diamox (250–500 mg/day) were evaluated in 30 HF patients for whom Diamox was added as de-novo/add-on decongestion therapy for acutely worsening HF ($n=18$) or as modification therapy for serum hypochloremia in stable HF (<100 mEq/L; $n=12$). Peripheral hematologic tests were performed at baseline, and at short- (≤ 10 days) and long-term (~ 60 days) time-points. In all 30 study patients of both groups, the serum chloride concentration increased in the short-term and even further over the long-term. The serum potassium concentration constantly decreased throughout the study period. Both the blood urea nitrogen and serum creatinine concentrations increased in the short-term, but returned to baseline levels over the long-term. Responders to Diamox ($n=13$; defined by HF resolution and body weight loss ≥ 1 kg) in the decongestion group exhibited reduced serum b-type natriuretic peptide levels and a markedly increased serum chloride concentration, but the hemoglobin/hematocrit and serum creatinine concentrations did not change after treatment. In conclusion, acetazolamide is a potent candidate "chloride-regaining diuretic" for treating HF patients under the "chloride theory". Its effect to enhance the serum chloride concentration occurred within 10 days and persisted for at least ~60 days. Plasma volume and renal function were preserved under adequate diuretic treatment with acetazolamide.

Keywords Heart failure · Chloride · Diuretics · Acetazolamide · Diamox · Electrolyte

Introduction

Along with the already established role of the electrolyte sodium [1–3], an important role of chloride in heart failure (HF) pathophysiology was recognized in the last several years. Some studies have strongly and independently noted the prognostic importance of hypochloremia in patients with chronic HF [4, 5]. My previous findings that chloride is a key electrolyte that regulates plasma volume during worsening HF [6] and its recovery following treatment with conventional diuretics [7] led me to propose the "chloride theory" for HF pathophysiology [8, 9] and to create a diuretic strategy that is based on modulating the serum chloride concentration in decompensated HF patients [9]. Early studies demonstrated that chloride-supplementary [10] or retaining therapy using a carbonic anhydrase inhibitor acetazolamide [11–14] might be effective for patients with refractory HF. This diuretic has long been outside of the mainstay decongestive treatment for worsening HF [15–17]. Based on the "chloride theory" for HF pathophysiology [9], manipulation of the serum chloride concentration using acetazolamide could become an attractive therapeutic target for HF treatment, as described in my recent reports [18, 19]. Therefore, the aim of the present study was to clarify the short- and long-term effects of a carbonic anhydrase inhibitor on changes in blood chemistry, particularly the serum chloride concentration, under add-on use of this agent to correct hypochloremia in patients with stable HF or to control worsening HF to determine its pharmacologic role under the "chloride theory" for HF pathophysiology [9].

✉ Hajime Kataoka
hkata@cream.plala.or.jp

[1] Internal Medicine, Nishida Hospital, Tsuruoka-Nishi-Machi 2-266, Saiki 876-0047, Oita, Japan

Methods

Study design

The present study was a single-center observational study to evaluate the effects of acetazolamide (Diamox) on the serum chloride concentration and other hematologic tests over short- and long-term time periods. The total study period was from February 2016 to September 2017, during which Diamox was prescribed and its efficacy to correct hypochloremia or for decongestion was evaluated in stable or acutely decompensated HF patients. The study protocol was approved by the ethics committee at Nishida Hospital. Informed consent was obtained from all patients before study enrollment.

Study patients

From among chronic stable or acutely decompensated HF patients who were followed up at the outpatient HF clinic of Nishida hospital, the present study enrolled 37 consecutive patients prescribed Diamox. Most of the study patients had at least one decompensated HF episode and regularly visited the outpatient clinic for monitoring of HF status and decongestion treatment with conventional diuretics and/or an oral vasopressin antagonist. In the present analysis, HF patients with severe renal failure (serum creatinine concentration > 3.5 mg/dL at stable HF status) were excluded.

Treatment protocol and data collection

Hyponatremia and hypochloremia were ordinarily defined as a serum sodium concentration of ≤ 135 mEq/L [20] and a serum chloride concentration of ≤ 96 mEq/L [4, 5], respectively. In the present study, for treatment aimed at correcting low serum chloride concentration (smaller than 100 mEq/L) in stable HF patients, or decongestion therapy in acutely worsening HF patients irrespective of the serum chloride level, a low-dose of Diamox (250–500 mg/d) was prescribed for each patient once or twice a day. The dose of Diamox was titrated up or down at my discretion based on blood test results and the patient's HF status. All the study patients underwent appropriate blood tests measuring hemoglobin, hematocrit, total protein, albumin, electrolytes, blood urea nitrogen, creatinine, and uric acid.

In acutely decompensated HF patients, HF-related physical sign(s), body weight, and serum b-type natriuretic peptide levels were checked at the initial presentation and appropriate intervals during the period of decongestion treatment with Diamox. A worsening HF event was defined as the appearance of at least one of the following HF-related signs whether or not there was a change in symptoms: physical signs of congestion (peripheral edema, pulmonary crackles, third heart sound), and/or pleural effusion on ultrasound [21, 22]. Based on a follow-up examination, I determined the optimal response to treatment for worsening HF and confirmed the clinical presentation of a return to stable HF status after therapy; responder to Diamox treatment was defined by resolution of HF-related sign(s) ≥ 1 and body weight loss ≥ 1 kg. If multiple examinations were performed during the study period, the latest available examination at the end of the short- (≤ 10 days) and long-term (≤ 60 days) time-points were selected for the analysis.

Statistical analysis

All statistical analyses were performed using commercially available statistical software GraphPad Prism 4 (San Diego, CA). All data are expressed as a mean ± SD for continuous data and percentage for categorical data. Paired and unpaired *t* tests for continuous data and Fisher's exact test for categorical data were used for two-group comparisons. A *p* value of less than 0.05 was considered statistically significant.

Results

Thirty-seven patients with mild–moderate HF that were prescribed Diamox completed the present study. To clarify the intrinsic effects of this agent, after excluding patients with replacement ($n = 3$) or combination usage ($n = 4$) at the initial prescription of this agent with other diuretic(s), I retrospectively analyzed 30 consecutive HF patients for whom Diamox was added as de novo/add-on modification therapy for serum hypochloremia (< 100 mEq/L; Modification group; $n = 12$) or decongestion therapy for worsening HF (decongestion group; $n = 18$). As such, in the selected 30 patients for the present investigation, background use of diuretics other than Diamox was absent (de-novo use of Diamox; $n = 3$) or continued at constant dosage (add-on use of Diamox; $n = 27$) 7 days before the initiation of Diamox and throughout the evaluation period of Diamox treatment to the time-point of short- (≤ 10 days) or long-time (~ 60 days).

The clinical characteristics immediately before Diamox treatment (Table 1), such as primary cause of HF, left ventricular ejection fraction, cardiac rhythm, and drugs used for HF treatment, were similar between groups except for dyspnea severity determined by the NYHA HF functional classification (unpaired *t* test and Fisher's exact test). As for blood tests obtained immediately before treatment (Table 2), hemoglobin and hematocrit were lower and the serum chloride concentration was higher in the Decongestion group than in the Modification group (unpaired *t* test and Fisher's

Table 1 Clinical characteristics of the study patients immediately before add-on Diamox treatment

Characteristics	Total ($n=30$)	Modification group ($n=12$)	Decongestion group ($n=18$)	p value
Age (years)				
Mean ± SD	84.6 ± 7.77	86.2 ± 5.46	83.6 ± 8.99	0.39
Range	53–97	80–97	53–94	
Male	9 (30)	2 (17)	7 (39)	0.25
Primary cause of HF				
Hypertension	19 (64)	8 (67)	11 (61)	1
Valvular	7 (23)	3 (25)	4 (22)	1
Ischemic/Cardiomyopathy	3 (10)	1 (8)	2 (11)	1
Arrhythmia	1 (3)	0	1 (6)	1
Left ventricular EF (%)				
Mean ± SD	58.0 ± 15.2	56.3 ± 15.8	59.1 ± 15.1	0.62
Left ventricular EF > 50%	21 (70)	7 (58)	14 (78)	0.42
Atrial fibrillation	11 (37)	5 (42)	6 (33)	0.71
NYHA-FC				
II	14	12	2	< 0.001*
III	11	0	11	
IV	5	0	5	
Concomitantly used drugs				
Diuretics				
Loop diuretics	20 (67)	9 (75)	11 (61)	0.69
Thiazide diuretics	7 (23)	1 (8)	6 (33)	0.19
MRA	17 (57)	6 (50)	11 (61)	0.71
Tolvaptan	6 (20)	2 (17)	4 (22)	1
ACE inhibitors/ARB	10 (33)	4 (33)	6 (33)	1
Beta-blockers	10 (33)	4 (33)	6 (33)	1
Calcium antagonists	12 (40)	5 (42)	7 (39)	1
Digitalis	1 (3)	1 (8)	0	1
Nitrates	1 (3)	1 (8)	0	1

Data presented as number (%) of patients otherwise specified. *ACE* angiotensin-converting enzyme, *ARB* angiotensin II receptor blocker, *EF* ejection fraction, *MRA* mineralocorticoid receptor antagonist, *NYHA-FC* New York Heart Failure functional class, *HF* heart failure. *Statistically significant

exact test). During the study period, the initial dosage of Diamox was kept constant except for in one study patient (Table 2).

Changes in blood test results during the short- and long-term periods in a total of 30 study patients in both groups are shown in Table 3 (paired t test). The serum chloride concentration increased in the short-term period and increased further in the long-term observation period. Hemoglobin and hematocrit did not change significantly during the study period. The serum sodium concentration did not change during the observational period, but the serum potassium concentration constantly decreased throughout both the short- and long-term study periods. Both blood urea nitrogen and serum creatinine concentrations increased during the short-term period, but returned to baseline levels over the long-term.

Table 4 shows the comparison of blood test results between the Modification and Decongestion groups (paired and unpaired t tests). In both groups, the serum sodium concentration was not changed, but the serum chloride concentration increased in the short-term and the long-term observation periods compared to the baseline (paired t test). Except for changes in the blood urea nitrogen and serum creatinine concentration during the short-term period in the Decongestion group, other blood test parameters were similar between groups: the blood urea nitrogen and serum creatinine concentration increased over the short-term period, but returned to the baseline level during the long-term period in the Decongestion group (paired t test).

Table 5 shows the comparison of clinical features and blood test results between responders ($n=13$) and non-responder ($n=5$) to treatment with Diamox in the Decongestion group. The number of HF-related signs, daily dose of Diamox, and duration of treatment were not different, but a greater reduction in body weight and serum b-type natriuretic peptide was achieved in responders (unpaired t

Table 2 Comparison of blood test results immediately before Diamox treatment, and Diamox dose between groups of modification therapy versus decongestion therapy

Variable	Modification group ($n=12$)	Decongestion group ($n=18$)	p value
Peripheral hematologic test			
Hemoglobin (g/dL)	12.4 ± 2.17	10.5 ± 1.73	0.001*
Hematocrit (%)	36.7 ± 6.08	32.0 ± 4.77	0.02*
Peripheral blood chemistry			
Serum sodium (mEq/L)	134 ± 3.93	138 ± 7.18	0.08
Serum potassium (mEq/L)	4.21 ± 0.66	4.07 ± 0.69	0.58
Serum chloride (mEq/L)	95.9 ± 2.23	102 ± 5.60	0.002*
Blood urea nitrogen (mg/dL)	22.1 ± 8.02	23.7 ± 11.3	0.67
Serum creatinine (mg/dL)	0.93 ± 0.39	1.07 ± 0.58	0.46
Serum uric acid (mg/dL)	6.68 ± 2.41	6.86 ± 2.76	0.86
Daily dose of Diamox (mg)	270 ± 72	347 ± 125	0.07
250 mg	11	11	
500 mg	1	6	0.17
250–500 mg	0	1	

*Statistically significant

test). In responders, the serum chloride concentration markedly increased after Diamox treatment (paired t test). Peripheral hemoglobin and hematocrit levels, and renal function determined by serum creatinine did not change after Diamox treatment (paired t test).

Discussion

The findings of the present study confirm that the carbonic anhydrase inhibitor acetazolamide, the oldest diuretic among commercially available carbonic anhydrase inhibitors, is a clinically potent candidate "chloride-regaining diuretic" for the treatment of HF patients under the "chloride theory" [9, 18]. Its effect to enhance the serum chloride concentration appears promptly within 10 days and persists for at least ~60 days. While achieving an adequate body weight reduction by diuresis for worsening HF status, diuretic treatment with this agent preserves plasma volume and renal function. Recently, my study also confirmed these effects in comparison with the conventional diuretic treatment for worsening HF; while both treatment groups exhibited equivalent body weight reduction and resolution of HF-related signs after each diuretic treatment, acetazolamide treatment preserved plasma volume and renal function compared to conventional diuretics [19].

Acetazolamide and its use under the "chloride theory" for HF pathophysiology

The carbonic anhydrase inhibitor acetazolamide has unique but critical diuretic actions: a "non-reabsorbable anion-like effect", that results in the excretion of bicarbonate $\left(HCO_3^-\right)$ into the urinary tubules with interchangeable absorption of filtrated chloride into the blood, and concurrent excretion of potassium into the urine [13, 16, 18]. An earlier study by Relman et al. [13] evaluated the acute effects (3–12 days) of acetazolamide treatment on serum solutes in 26 patients with severe HF (men, 73%; age, 56.7 ± 12.4 years) and found that the serum chloride concentration was increased in 78% of 27

Table 3 Changes in peripheral hematologic test and blood biochemistry results in all study patients ($n=30$) under Diamox treatment

Variable	Before ($n=30$)	Short-term (≤10 days) ($n=21$)	Long-term (11 to 60 days) ($n=28$)	p value		
				Before vs. short ($n=21$)	Before vs. long ($n=28$)	Short vs. long ($n=18$)
Peripheral hematologic test						
Hemoglobin (g/dL)	11.3 ± 2.10	10.9 ± 2.51	11.1 ± 2.14	0.18	0.28	0.15
Hematocrit (%)	33.9 ± 5.71	33.4 ± 7.09	33.5 ± 5.95	0.64	0.41	0.11
Peripheral blood chemistry						
Serum sodium (mEq/L)	137 ± 6.36	137 ± 4.56	138 ± 4.73	0.93	0.05	0.13
Serum potassium (mEq/L)	4.12 ± 0.67	3.81 ± 0.51	3.91 ± 0.61	0.02*	0.04*	0.77
Serum chloride (mEq/L)	99.4 ± 5.35	103 ± 3.91	105 ± 4.91	0.004*	< 0.0001*	0.04*
Blood urea nitrogen (mg/dL)	23.1 ± 9.99	26.0 ± 9.22	24.5 ± 9.49	0.004*	0.45	0.7
Serum creatinine (mg/dL)	1.01 ± 0.51	1.15 ± 0.62	1.05 ± 0.57	0.02*	0.24	0.26
Serum uric acid (mg/dL)	6.78 ± 2.58	7.02 ± 2.51	6.46 ± 2.37	0.78	0.28	0.046*

*Statistically significant

Table 4 Changes in peripheral blood test results between groups receiving *Modification Therapy* versus *Decongestion Therapy* from baseline to short- (≤ 10 days) or long-term (11–60 days) end-points after Diamox treatment

	Short-term	*p* value	Lon g-term	*p* value
Number of study patients				
Modification group	$n=10$	–	$n=11$	–
Decongestion group	$n=11$	–	$n=17$	–
ΔHemoglobin (g/dL)				
Modification therapy	− 0.22 ± 0.73	0.366	− 0.53 ± 0.84	0.06
Decongestion therapy	− 0.17 ± 0.58	0.35	0.024 ± 0.95	0.92
p value	0.87		0.13	
Δ Hematocrit (%)				
Modification therapy	− 0.35 ± 2.04	0.619	− 1.23 ± 2.34	0.11
Decongestion therapy	− 0.07 ± 1.84	0.9	0.1 ± 2.78	0.88
p value	0.75		0.2	
ΔSerum sodium (mEq/L)				
Modification therapy	0.4 ± 2.41	0.613	2.09 ± 5.52	0.24
Decongestion therapy	− 0.27 ± 2.61	0.74	1.24 ± 3.05	0.12
p value	0.55		0.6	
ΔSerum potassium (mEq/L)				
Modification therapy	− 0.17 ± 0.57	0.373	− 0.35 ± 0.65	0.1
Decongestion therapy	− 0.45 ± 0.59	0.029*	− 0.18 ± 0.60	0.24
p value	0.28		0.46	
ΔSerum chloride (mEq/L)				
Modification therapy	4.9 ± 1.91	< 0.0001*	7.73 ± 4.54	0.0002*
Decongestion therapy	3.45 ± 3.80	0.013*	4.65 ± 3.71	< 0.0001*
p value	0.29		0.06	
ΔBlood urea nitrogen (mg/dL)				
Modification therapy	3.0 ± 4.92	0.086	4.36 ± 8.51	0.12
Decongestion therapy	2.91 ± 3.65	0.025*	− 0.94 ± 6.86	0.58
p value	0.96		0.08	
ΔSerum creatinine (mg/dL)				
Modification therapy	0.05 ± 0.14	0.273	0.037 ± 0.19	0.54
Decongestion therapy	0.12 ± 0.17	0.049*	0.035 ± 0.14	0.3
p value	0.37		0.98	
ΔSerum uric acid (mg/dL)				
Modification therapy	− 0.46 ± 0.96	0.164	− 0.73 ± 1.16	0.065
Decongestion therapy	0.55 ± 1.12	0.13	− 0.11 ± 1.98	0.82
p value	0.039*		0.36	

Δ = change from baseline (before treatment) to the point of short- (≤10 days) or long-term after Diamox treatment

*Statistically significant

evaluations, the serum sodium concentration was unchanged or increased in 73% of 24 evaluations, and the serum potassium concentration was decreased in 73% in 22 evaluations. The results of the present study of the short-term effects of acetazolamide on serum electrolytes are similar to those reported by Relman et al. [13]. Additionally, the present study disclosed the long-term effects of acetazolamide treatment on serum electrolytes: the serum chloride concentration increased in the short-term and increased even further during the long-term period, and serum potassium concentration constantly decreased throughout the study period. More importantly, plasma volume and renal function were preserved under adequate diuretic treatment with acetazolamide, as in diuretic therapy using a vasopressin receptor antagonist [23, 24], in accordance with the "chloride theory" for HF pathophysiology [9]. Acetazolamide treatment might provide successful decongestion effects while minimizing changes in vascular volume, renal function, and neurohormonal activation by enhancing the serum tonicity with chloride [9, 19, 24]. On the other hand, it should be kept in mind that diuretic therapy for the retention or supply of chloride in the plasma may sometimes induce a smaller

Table 5 Responders versus non-responders in the Diamox decongestion group

Variable	Responders ($n=13$)	Non-responders ($n=5$)	p value
Age (years)	82.7 ± 10.3	85.6 ± 4.16	0.56
HF-related signs	1.85 ± 0.9	1.40 ± 0.55	0.32
Daily dose of Diamox (mg)	365 ± 130	300 ± 112	0.34
Treatment duration (days)	27.6 ± 12.7	38.0 ± 17.5	0.18
Body weight (kg)			
Worsening	44.0 ± 10.5	53.5 ± 13.5	0.13
Δchange after therapy	− 2.23 ± 1.11	− 0.20 ± 0.63	0.0016*
p value	< 0.0001*	0.51	
Serum log BNP (pg/mL)			
Worsening	2.33 ± 0.45	2.36 ± 0.19	0.88
Δchange after therapy	− 0.24 ± 0.26	− 0.11 ± 0.14	0.31
p value	0.012*	0.16	
Hemoglobin (g/dL)			
Worsening	10.2 ± 1.89	11.3 ± 1.11	0.25
Δchange after therapy	0.03 ± 0.96	0.1 ± 0.96	0.89
p value	0.91	0.83	
Hematocrit (%)			
Worsening	31.4 ± 5.25	34.0 ± 2.76	0.33
Δchange after therapy	0.19 ± 2.91	0.46 ± 2.76	0.86
p value	0.82	0.67	
Serum sodium (mEq/L)			
Worsening	139 ± 7.18	137 ± 7.19	0.53
Δchange after therapy	1.0 ± 4.22	2.40 ± 2.88	0.51
p value	0.41	0.14	
Serum potassium (mEq/L)			
Worsening	3.85 ± 0.60	4.46 ± 0.74	0.09
Δchange after therapy	− 0.24 ± 0.63	− 0.14 ± 0.56	0.76
p value	0.2	0.61	
Serum chloride (mEq/L)			
Worsening	102 ± 5.33	102 ± 6.72	0.99
Δchange after therapy	5.31 ± 4.91	3.40 ± 4.10	0.45
p value	0.002*	0.14	
Blood urea nitrogen (mg/dL)			
Worsening	23.5 ± 12.0	23.6 ± 10.8	0.99
Δchange after therapy	0 ± 6.19	− 4.2 ± 6.42	0.22
p value	1	0.22	
Serum creatinine (mg/dL)			
Worsening	1.11 ± 0.66	0.94 ± 0.34	0.59
Δchange after therapy	0.048 ± 0.12	0.04 ± 0.19	0.91
p value	0.19	0.66	
Serum uric acid (mg/dL)			
Worsening	7.02 ± 2.86	5.92 ± 2.97	0.48
Δchange after therapy	0.046 ± 1.13	− 0.48 ± 3.45	0.62
p value	0.89	0.77	

BNP b-type natriuretic peptide, *HF* heart failure

*Statistically significant

reduction in cardiac volume in relation to cardiac function, thus ensuring a persistent burden on the heart [9, 19, 24]. In the case of a persistent cardiac burden even under adequate diuretic therapy for unloading the heart, strategies to further reduce the cardiac burden or enhance cardiac power would be required in parallel, such as using inotropes, controlling

blood pressure and heart rate, modulating cardiac re-synchronization, and ultrafiltration [25].

Mineralocorticoid receptor antagonists are recommended for HF patients [26], but they are under-prescribed and frequently discontinued mainly when hyperkalemia develops [27]. Under such situations, however, the potassium-lowering actions of acetazolamide could provide enough ability for administration of a mineralocorticoid receptor antagonist [15], as is confirmed in the present study. Monitoring the changes in the serum potassium concentration from the beginning of acetazolamide treatment is, of course, very important after introducing this diuretic treatment because hypokalemia may appear promptly, as shown in the present study ($\leq$10 days) and the report by Relman et al. (3–12 days) [13]. The development of hypokalemia should be corrected by adding or increasing the dose of mineralocorticoid receptor antagonists and/or a potassium supplement [28, 29] to avoid serious events of malignant ventricular arrhythmias [29].

Other important and beneficial aspects of acetazolamide

The target level for correcting the serum chloride concentration with acetazolamide treatment is not yet clear, and must be determined to resolve the presumed harmful effects of the retention of excess serum chloride retention [30–32] in HF pathophysiology. Other than the expectation of hemodynamic effects reported in the present study, acetazolamide has advantageous effects to improve the central type of sleep-disordered breathing [33, 34], which is a frequent complication in patients with advanced HF status [35].

Various acid–base disorders appear in HF status: about 37% of HF patients show at least one acid–base abnormality, most commonly metabolic alkalosis, alone or associated with respiratory alkalosis [29]. As both blood alkalosis and urine acidosis may worsen the prognosis of HF patients [36–38], acetazolamide could be beneficial in many HF patients because this agent can correct metabolic alkalosis by repletion of serum chloride and enhancement of renal bicarbonate excretion [18, 29].

Interestingly, my experience described in the recent case report noticed that acetazolamide may have a potential for correcting hyponatremia, indicating that acetazolamide could be an alternative diuretic to vasopressin antagonists for some proportion of HF patients with hyponatremia [39].

Side effects of acetazolamide

Rare but serious side effects are associated with the use of acetazolamide. For example, acetazolamide is a sulfonamide derivative and, like other sulfonamides, may cause bone marrow depression, skin toxicity, and allergic reactions in patients hypersensitive to sulfonamides [40, 41]. In HF patients with renal failure, acetazolamide causes blood acidosis by blocking renal carbonic anhydrase [36] and the progression of blood acidosis might worsen preexisting renal dysfunction [42]. In patients with severe liver dysfunction, this agent may increase the level of circulating ammonia and worsen hepatic disturbances [43].

Limitations

This study included a small number of patients at a single center, and there are important limitations to consider, including (1) a selection bias due to data availability and (2) low statistical power with wide variabilities in the data. Thus, the data must be cautiously interpreted. Additional well-designed large trials are required to confirm the findings of the present study and to re-evaluate the effects of the forgotten, but indispensable, diuretic agent acetazolamide, on the pharmacologic, hemodynamic, and neurohormonal aspects, as well as the acid–base balance and prognosis of HF pathophysiology.

Conclusion

Acetazolamide is a potent candidate "chloride-regaining diuretic" through the exchange between chloride and bicarbonate in the nephron [13, 16, 18] for treating HF patients under the "chloride theory" [9]. Its effect to enhance the serum chloride concentration occurred within 10 days and persisted for at least ~60 days. Plasma volume and renal function were preserved under adequate diuretic treatment with acetazolamide.

Compliance with ethical standards

Conflict of interest The author declares that he has no conflict of interest.

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