EDITORIAL

Acetazolamide as a potent chloride-regaining diuretic: time to re-evaluate its diverse actions

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Received: December 1, 2023.
Accepted: December 4, 2023.
Published online: December 21, 2023.
Pol Arch Intern Med. 2023; 133 (12): 16629
doi:10.20452/pamw.16629

Salt (sodium chloride) is the most abundant mineral in the human body. To date, research on pathophysiology and diuretic treatment of heart failure (HF) has been mostly focused on the role of sodium and water. Over the last several years, however, chloride has been recognized to play an important role in the prognosis of patients with HF[1] and pathophysiology of the disease.[2] During that period, I proposed a hypothesis for HF pathophysiology named the "chloride theory." It states that changes in the serum chloride concentration are strongly associated with changes in plasma volume, hemodynamics, and neurohormonal activity during worsening of HF and its therapeutic resolution.[2] This hypothesis led me to create a new classification of diuretics, based on their effect on the serum chloride concentration and subsequent change in plasma volume via tonicity-related water movement,[3] as concisely summarized in TABLE 1. Accordingly, timely adjustment of diuretic combinations and doses during the clinical course of HF treatment is appropriate for vascular volume control (to reduce cardiac burden with chloride-depleting diuretics), and for drainage of tissue edema into the vascular space (to restore organ function with chloride-regaining diuretics).[3] Acetazolamide, the most potent chloride-regaining diuretic classified in TABLE 1, is expected to exert its diuretic effect by increasing serum chloride concentration and thereby serum tonicity, thus facilitating redistribution of water from the interstitial space to the vascular space, and maintaining organ function.[2-4]

Recently, the ADVOR (Acetazolamide in Decompensated Heart Failure with Volume Overload) trial[5,6] showed that the addition of an intravenous dose of acetazolamide to loop diuretic therapy in patients with acute HF results in a higher incidence of successful decongestion. In this issue of *Polish Archives of Internal Medicine*, Kosiorek et al[7] provide clinical data supporting the diuretic effect of oral acetazolamide in a prospective, randomized, single-blind (participants) study, thus confirming the results of previous smaller studies[3,4] and providing evidence for its widespread clinical use. Furthermore, the study deepens our knowledge on favorable effects of acetazolamide on the kidney by examining the specific effects of the drug on the renal function. Similarly to a previous study,[8] Kosiorek et al[7] reported preserved renal function in patients treated with oral acetazolamide. More importantly, they confirmed reduced renal damage with acetazolamide by analyzing the urinary renal biomarkers, such as neutrophil gelatinase–associated lipocalin, renal injury molecule-1, and cystatin C, thus indicating that this diuretic is safe to use in the treatment of HF. The favorable effects of acetazolamide on the kidney reported by Kosiorek et al[7] may be related to the drug's pharmacologic effects via modulation of chloride kinetics under HF conditions,[3,4,8] which need to be confirmed by future studies.

As an electrolyte, chloride has been shown to play many physiologic roles in the human body[9]: 1) it is the most important extracellular anion, accounting for 97% to 98% of all strong anion charges and for two-thirds of all negative charges in the plasma; 2) it maintains serum electroneutrality; 3) it is the major extracellular strong ion and the key electrolyte for maintaining the acid-base balance; 4) it contributes to electrical activity in general (eg, muscular and myocardial activity); 5) it contributes to hydrochloric acid production, maintenance of osmotic gradient, and fluid secretion in the gastrointestinal tract; 6) it affects oxygen transport and gas exchange; 7) it contributes to the maintenance of blood pressure and renal function; and 8) it contributes to the movement of water between fluid compartments. Some of these actions of chloride could,

TABLE 1 Classification of diuretics by their effect on the serum chloride concentration, as proposed by Kataoka[3]

Serum chloride concentrations	Mechanism of action according to the "chloride theory"
Decremental direction (chloride-depleting diuretics)	
• Loop diuretics	Reduce vascular tonicity to decrease plasma volume and reduce cardiac load
• Thiazide diuretics	
Incremental direction (chloride-regaining diuretics)	
• Carbonic anhydrase inhibitor (acetazolamide)	Increase vascular tonicity to promote return of excess interstitial fluid to the vascular space and reduce organ damage/dysfunction
• Aquaretic diuretics (V2-receptor antagonists)	
• Sodium-glucose cotransporter 2 inhibitors	
Neutral	
• Mineralocorticoid-receptor antagonists	–

to a greater or lesser extent, contribute to HF pathophysiology. Therefore, HF treatment targeting electrolyte chloride with acetazolamide is expected to modify HF progression through possible mechanisms discussed by Kosiorek et al[7] in this issue of the journal. For example, treatment with loop/thiazide diuretics often induces hypochloremia, exacerbating the diuretic effects.[10] It may also promote metabolic alkalosis, inducing reduced respiratory activity and carbon dioxide retention,[11] resulting in a vicious cycle of worsening HF. Treatment with a chloride-regaining diuretic, such as acetazolamide, can disrupt this vicious cycle by correcting hypochloremia and metabolic alkalosis. Furthermore, this drug also corrects hyponatremia,[12] which often occurs in refractory HF. Thus, despite being an old diuretic, acetazolamide may once again become an effective option for HF treatment, and it is time to re-evaluate its diverse pharmacologic effects.

On another note, the respective electrolytes, sodium and chloride, play an important role in the pathophysiology of HF. For instance, extensive water-independent Na^+ stores have been reported in the dermal interstitial space, and thus the natriuretic response, rather than the chloruretic response, may be a useful prognostic marker in HF.[13,14] We should pay more attention to the similar, but also distinctly different, roles of these electrolytes in the pathophysiology of HF by conducting comparative studies.[15,16] Given that the serum chloride concentration, but not the sodium concentration, has been reported to be an independent prognostic marker in patients with acute and chronic HF,[1,10] future studies are needed to determine whether correction of hypochloremia with acetazolamide can improve HF prognosis.[10]

ARTICLE INFORMATION

DISCLAIMER The opinions expressed by the author(s) are not necessarily those of the journal editors, Polish Society of Internal Medicine, or publisher.

CONFLICT OF INTEREST None declared.

HOW TO CITE Kataoka H. Acetazolamide as a potent chloride-regaining diuretic: time to re-evaluate its diverse actions. Pol Arch Intern Med. 2023; 133: 16629. doi:10.20452/pamw.16629

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