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Actuality of the use of acetazolamide as a diuretic: usefulness in refractory edema and in aldosterone-antagonist-related hyperkalemia*

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** This is the last article published in Nefrología by Dr. Carlos Caramelo Díaz. It is an article that is published after he passed away as if his enormous scientific productivity would have wanted to trick the time and place in another dimension the continuity of his professional activity. Many of us knew Carlos precisely for his work and educational activity. Others were more fortunate to work with him and share ideas, euphoria and disheartening. Carlos was a nephrologist full of responsability and good working. He always was generously prone to collaborate, especially with young nephrologists. Many of the ones training with him are nowadays a reference to our Society, even if they are young. They gathered science and humanity and they will pass Carlos' mastership to new generations. However, this trich to time is just the last play of this nephrologist from Buenos Aires. This article is the firs step for his eternal presence.*

A. L. M. de Francisco
President of the SEN

Carlos Quereda
Director of Nefrología

Acetazolamide (ACZ), a sulphonamide derivative, is the oldest diuretic among those commercially available. Although uncommon nowadays, its use has survived due to its usefulness in glaucoma rather than for its diuretic properties.[1]

Its role in edema management has been limited because of two essential facts: the induction of metabolic acidosis because of renal bicarbonate loss and the compensating reabsorption effect at distal segments, which preclude its complete use, as shown in figure 1. These circumstances limit its use and imply a particular issue on its management. However, our opinion, based on recent clinical experiences and on literature data, is that ACZ has a more relevant role than just the usual one for edematous syndromes, and particularly in heart failure (HF). Besides, the comments that we make on ACZ underscore once again the classical statement that HF can never be considered refractory until *sufficient and effective* combinations of diuretics have been used.

The points that we highlight are more clearly shown through the following real clinical cases treated during the last year.

CASE 1

This is a 75-years old female with repeated admissions for HF and a personal history of AHT, type 2 DM, AF, and pacemaker placement, pulmonary hypertension, tricuspid regurgitation, and mild RF. She was admitted again because of decompensation, with pO2 of 54 mmHg, oliguria and anasarca, progressive edemas of the lower limbs, pleural and pericardial effusion. The laboratory work-up showed K_P^+ 6.4 mEq/L, Na^+ 134 mEq/L, creatinine 4.3 mg/dL. Venous blood gases showed pH 7.42 and bicarbonate 22.1 mEq/L. She was treated by means of continuous infusion furosemide pump, with a poor diuretic response and persistent hyperkalemia of K_P^+ 7 mEq/L, and severe Na^+ retention -Na^+ p/u ratio of 126/22 mEq/L. Given the bad clinical situation, a blockade of the different clinical segments with ACZ, furosemide, and hydrochlorotiazide was started. Pulsed doses of 1M bicarbonate were given to keep bicarbonate levels above 22 mmol/L. The clinical improvement and diuretic response were remarkable, with a negative balance of 30 liters in 20 days, normalization of potassium levels, and creatinine decrease to 1.3 mg/dL. This case is remarkable for the magnitude of the diuretic response that was only achieved with multi-segmentary tubular blockade.

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CASE 1

This is a 71-years old woman with DM, mitral valve prosthesis due to stenosis, severe tricuspid valve regurgitation, slow-pace AF, a pacemaker, and pulmonary hypertension. She was admitted for congestive HF, receiving therapy with furosemide, spironolactone and captopril. During the admission she presented diarrhea, followed by syncope and severe bradycardia. The EKG, which we show because of its educational value (fig. 2), showed capture failure of the pacemaker and

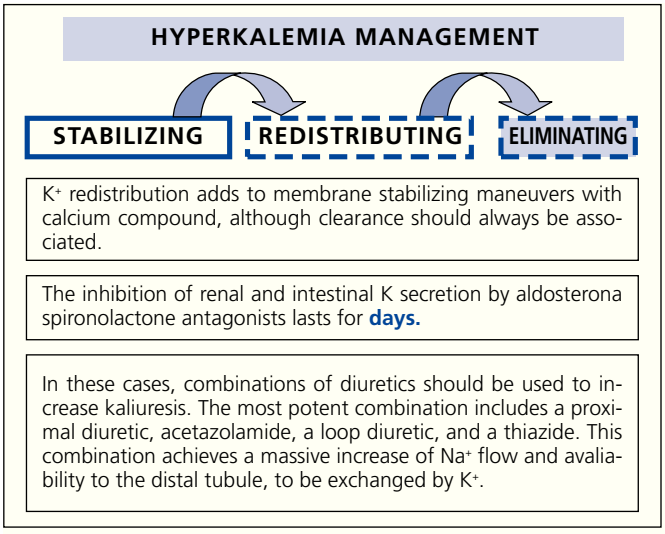

Figure 1. Hyperkalemia management is particularly complex if there is competitive inhibition of the aldosterone by specific drugs.

pointed T waves. The laboratory workup showed K_p^+ of 8.6 mEq/L. She was treated with i.v. calcium gluconate, insulin, and dextrose fluid, recovering the myocardial activity although with persistent pathological potassium unbalance (K^+ p/u = 7/14 mEq/L) after 12 hours of therapy. Thus, ACZ and pulsed sodium bicarbonate 1M were added, achieving a change in potassium management (K^+ p/u = 4.1/54 mEq/L) within the following 24 hours.

Again, and as in case 1, the use of bicarbonate is the differential critical element since it provides ACZ its «*working material*» and allows perpetuating its effect. The interest of this case is centered in the use of ACZ as a promoting factor for K^+ clearance, boosted by adding bicarbonate that counteracts its acidifying effect.

CASE 3

This is a 91-years old man, hypertensive, with a personal history of operated colon cancer, pneumonia and iron deficient anemia. He consulted for progressive weakness of the lower limbs for several days after substitution of thiazide with spironolactone. Severe hyperkalemia (K^+ 9.6 mEq/L), metabolic acidosis (plasma bicarbonate 12.8 mmol/L) and creatinine of 1.5 mg/dL, with pointed T waves at the EKG, were detected.

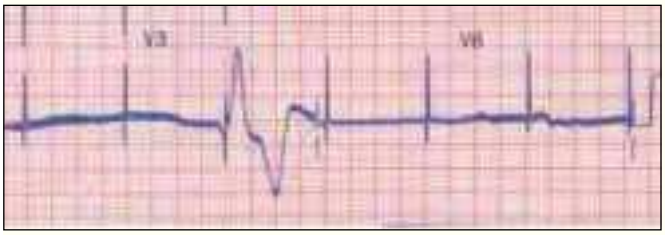

Figure 2. Capture failure of the pacemaker. Note the appropriate pacemaker firing although with ventricular refractoriness caused by severe hyperkalemia.

After treatment with calcium gluconate, insulin and bicarbonate he recovered his mobility although with persistent hyperkalemia and low K^+ p/u = 8.3/22 mmol/L. ACZ was started and, as in the previous cases, the bicarbonate level was maintained with pulsed doses (50 mmol) of sodium bicarbonate 1M, with normalization of potassium management (4.2/64 mmol/L) within 24 hr.

As in the previous case, this one illustrates a practical way of achieving kaliuresis in spite of distal blockade of K^+ clearance caused by anti-aldosterone agents. The initial acidosis was not an obstacle for using ACZ, by counteracting the potential negative effect with the use of bicarbonate.

CASE 4

This is a 76-years old woman, with a previous history of AHT, DM, dyslipemia, morbid obesity, chronic AF, dilated cardiomyopathy with several admissions for HF, chronic respiratory failure, hypothyroidism, and anemia. She was admitted for shortness of breath at minimal efforts and anasarca. The plasma creatinine values were 0.66 mg/dL, sodium 121 mEq/L, potassium 3.6 mEq/L, bicarbonate 22 mEq/L. She was first treated with loop-diuretics and water restriction, with a poor diuretic response, presenting 72 hr later oliguria of 480 mL/24 h, with persistent edematous condition and dyspnea worsening. Because of the lack of response to furosemide, we induced complete tubular blockade with ACZ, furosemide, hygroton, and spironolactone; because of the existence of hyponatremia, 100 mmols of i.v. bicarbonate 1M were infused achieving an increase in plasma level to 26 mEq/L. A significant clinical improvement was achieved within 48 hours, with a negative fluid balance of 2 liters, with a sustained trend until resolution of anasarca within 10 days, and associated normalization of water and electrolytes parameters. IV bicarbonate was continued titrating the dose as necessary to keep plasma levels ≥ 22 mmol/L (30-50 mmols/day). Figure 3 shows the dramatic increase in natriuresis when using the diuretics association, clearly higher than the amount of bicarbonate administered. It is interesting to see how spironolactone modulates the kaliuretic effect of ACZ, thus preventing excessive Kp depletion.

PROBLEMS THA MAY BE RESOLVED BY USING ACZ-CONTAINING DIURETIC ASSOCIATIONS

The main applications of ACZ, which we illustrate in the cases, are refractory edema and hyperkalemia in the presence of aldosterone blockade. Other authors have also successfully used this therapy for chloride depletion-induced alkalosis, mountain sickness, and sleep apnea associated to heart failure.[2-4]

In the first case, we refer to the so-called true refractory edema and not to the one caused by dietary transgressions or lack of adherence to prescribed drugs. Resistance to diuretic therapy may occur in multiple edematous states and is generally due to the occurrence of tubular adaptative changes with

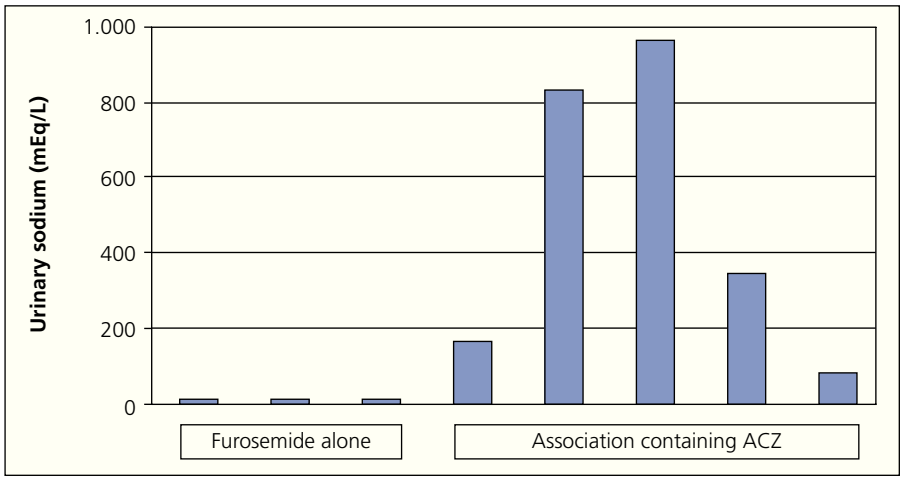

Figure 3. Effects of the acetazolamide (ACZ)-containing diuretic association on sodium urinary clearance in a patient with refractory edema.

overexpression and/or induction of the transporters activity that are inhibited by diuretics. These adaptations take place at different times, immediately through the direct stimulus of Na^+ reabsorption at segments distal from the diuretic site of action, with post-diuretic ClNa retention, and in the long run with the so-called *«braking phenomenon»*.[5,6] In these circumstances, the combination of diuretics acting at different tubular segments has been shown to be extremely effective, even in patients with clearly adverse circumstances for initiating diuresis. Although the combination of a loop diuretic and a thiazide is the one most commonly used, adding diuretics acting on different segments is a superior alternative.[7,8] Thus, by notably increasing the fluid amount at the Henle's loop, ACZ acts as an enhancer of the furosemide action. Adding a thiazide and a distal diuretic ensures diuretic coverage of all nephron segments. It may be that in the future a fifth element will be added to this combination, the V2 vasopressin antagonist, which has an exclusive action on water transport at the collecting tubule.

In the particular case of HF, the diuretic response is markedly correlated with low pre-treatment sodium fractional excretion (Na^+FE). This is particularly evident in patients with Na^+FE markedly below the normal range (< 0.2%). Proximal Na^+ reabsorption, which is conditioned by the decrease in effective circulating volume, is the major determinant in resistance to diuretics in edematous diseases with functional underfilling of the vascular system. Cases 1 and 4 clearly show how the quadruple association works in patients in whom a simpler diuretic regime would have failed. In this scheme, instead of an aldosterone-antagonist, we may have used a Na:K channel blocker, such as amiloride or triamterene; however, aldosterone antagonism brings additional properties on the cardiovascular system and tissue potassium redistribution, which are absent with Na:K channel blockers; besides, the Spanish pharmacopoeia lacks of preparations of these latter drugs free from thiazides. Among aldosterone antagonists in the market, the current trend is to preferentially use eplerenone (Elecor®) because of the lack of anti-androgenic effect. Recent studies have fully confirmed the therapeutic value of eplerenone.[9-12]

The second aspect making the application of ACZ more up-to-date relates with the marked increase in the frequency of hyperkalemia associated with competitive inhibi-

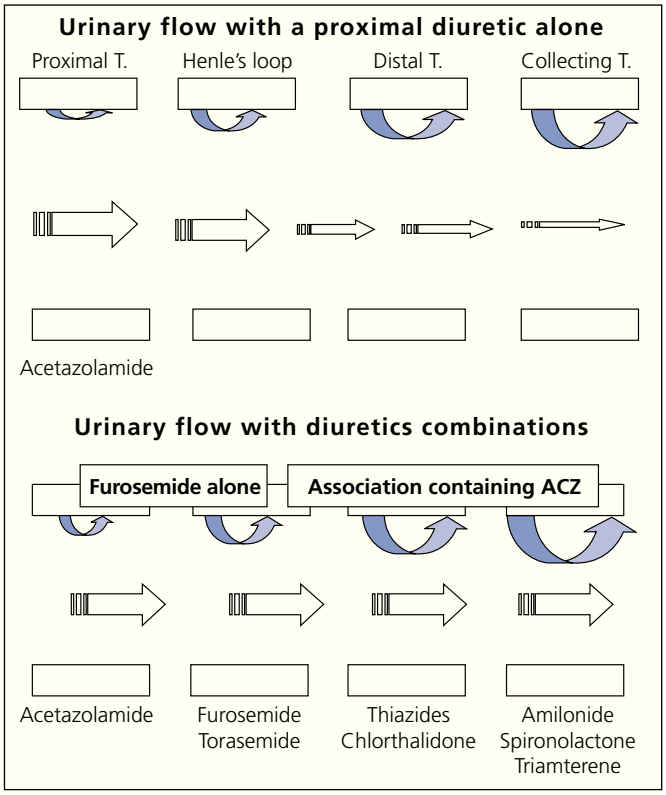

Figure 4. Effect of the association of diuretics: if used alone, the effect of a proximal diuretic such as ACZ fades due to reabsorption at more distal segments (top of the figure). However, if diuretics with actions on successive segments are used, the proximal effect is maintained achieving a much more abundant diuresis. This is particularly important in conditions, such as heart failure, where proximal reabsorption is maximally stimulated.

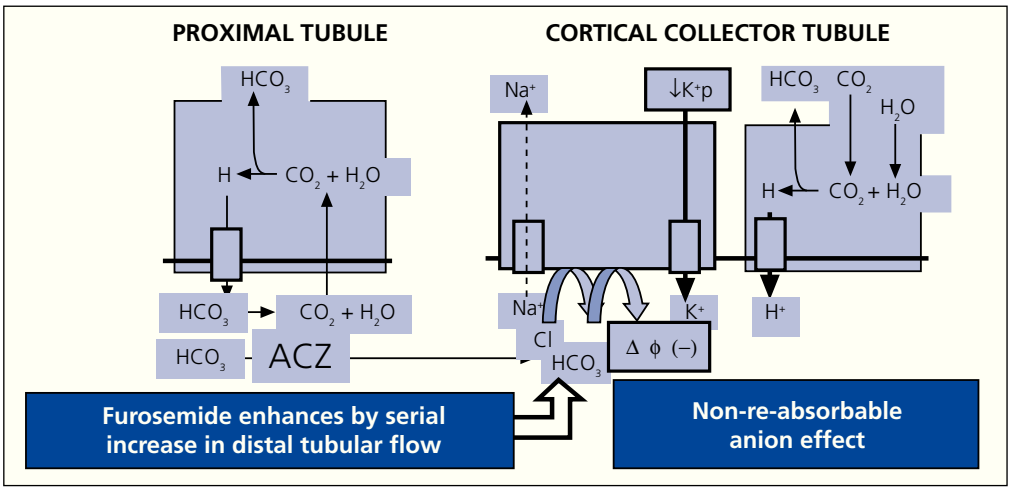

Figure 5. Bicarbonate, acetazolamide and furosemide for hyperkalemia control. ACZ produces a «non-re-absorbable anion-like» effect. The key element in this type of actin is the increase in the electrical neutrality within the lumen at the distal segments and cortical collecting segments, with the subsequent trapping and dragging of Na^+ y K^+. From there are derived the natriuteric and kaliuretic effects mentioned in the text. This effect is quantitavely enhanced in the presence of diuretics with an action on other segments, in particular loop diuretics. ACZ = acetazolamide.

tion of aldosterone receptors, a direct consequence from the publication of the RALES study.[13-16] This kind of hyperkalemia is difficult to resolve, requiring even extracorporeal depuration techniques since the blockade of potassium urinary clearance by anti-aldosterone agents is prolonged for days. The use of an ACZ-containing association achieves the induction of potassium excretion though a non-re-absorbable anion effect, as illustrated by cases 2 and 3. Figure 4 shows a scheme of the mechanism by which this occurs. In this setting, the combination that we propose may be extremely useful for relieving a substantially irresolvable situation.

USE OF ACETAZOLAMIDE

ACZ has not been considered as a first-line drug because of the above-mentioned limitations. The efficacy of ACZ linearly decreases when plasma bicarbonate levels lower than normal are reached. By contrast, its action is complete in the presence of high bicarbonate levels, so that it is a very interesting complementary drug when thiazides or furosemide are used, especially at high doses, rendering these patients particularly susceptible to alkalosis. Thus, as we have already mentioned, ACZ has been used in chloride-induced alkalosis; in this sense, it is important and of practical application to remember that the use ACZ for this purpose does not need daily doses and can be used as a two-to-three times a week regimen.

The main aspect to highlight is that although ACZ is naturally most effective under alkalosis conditions, its effect may be induced by keeping normal bicarbonate levels by infusing controlled amounts of i.v. bicarbonate, as shown in the cases presented. Under this circumstance, the need for associations to achieve a complete effect is obvious; in addition to ACZ, these associations should include a loop diuretic and a thiazide. Adding or not a distal diuretic will depend on the desired effect, either edema or potassium clearance, respectively.

ACTION, PHARMACOLOGY AND POSSIBLE ADVERSE EFFECTS OF ACETAZOLAMIDE

ACZ acts by inhibiting carbonic anhydrase, mainly located on the apical and basolateral basement membranes and within the lumen of the proximal tubule, inducing natriuresis, kaliuresis, and bicarbonaturia (fig. 5). Figure 5 specifically shows the effect of ACZ on urinary bicarbonate.

ACZ absorption is rapid, achieving maximal concentrations p.o. within 2 hours, with a half-life of approximately 12 h. The usual dose is 250-500 mg every 12-24 h. When associated to loop diuretics the recommended dose is 500 mg p.o. of ACZ 2 hours before the intake of the loop diuretic.

A key resort, seldom used but effective, consists in *«priming»* the mechanism with i.v. bicarbonate; colloquially speaking, we may say that a certain amount of Na^+ is «bid» as bicarbonate in order to recover considerably more. The bicarbonate keeps ACZ active by allowing persistent bicarbonaturia and the subsequent tubular fluid dragging. From the point of view of the effectiveness of HF-related edema management, and always considering that salt restriction is being carried out, our recommendation is sequentially adding diuretics, provided that time and severity allow for it, according to the following scheme: i) Starting with thiazide if CrCl is > 50 mL/min, or with furosemide if CrCl is lower; ii) associating both; iii) adding an aldosterone antagonist; iv) adding ACZ. This sequence allows achieving high Na^+FE values (5% or higher). Taking into account that under the same circumstance the EFK may be of about 70%, an evident risk from combining diuretics is hypokalemia. This may be partially limited with the use of Na:K channel blockers, such as amiloride, or with aldosterone antagonists, although the key point is the use of K supplements in quantities equivalent to urinary losses.

In summary, the present work brings ACZ, an unnecessarily forgotten diuretic, to an important plane for direct application in conditions of the current cardiologic practice. We definitely recommend its use in HF-related refractory edema, hyperkalemia secondary to aldosterone blockade, and in diuretic-associated alkalosis.

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