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ASSESSMENT OF THE TUBULAR HANDLING OF POTASSIUM IN CIRRHOTIC PATIENTS TREATED WITH A COMBINATION OF FUROSEMIDE + SPIRONOLACTONE

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SUMMARY:

Cirrhotic patients develop hyperaldosteronism secondary to advanced stages of their illness and require treatment with furosemide + spironolactone. The tubular handling of potassium (K) in this patients under such combined diuretic scheme (antagonic) had not yet been studied, therefore we decided to document in an original way the net effect, in this pharmacological context, of the renal potassium handling assessed by means of two specific indicators for that purpose: the fractional excretion of potassium (FEK) and the transtubular potassium gradient (TTKG).

Material and Method: The FE of sodium (Na), FEK and TTKG were assessed in 18 patients (11 men), with an average age of 56, normokalemic, suffering from compensated cirrhosis (Ci) stages Child Pugh A, B and C, MELD 22, having normal glomerular filtration, urinary sediment and renal ultrasound, treated with furosemide (average dose: 40 mg/day) + spironolactone (average dose: 100 mg/day) and on hyposodic diet. The control group consisted of 10 healthy volunteers under the same diet (S). For the statistical analysis of the data, the non-parametric test Wilcoxon was applied.

Results: Kalemia (mmol/l): 4 ± 0.5 (Ci) vs. 4 ± 0.3 (S), p=NS; FENa (%): 0.8 ± 0.4 (Ci) vs. 0.5 ± 0.3 (S) p=NS; FEK (%): 9.1 ± 3 (Ci) vs. 10 ± 2 (S), p=NS; TTKG: 6 ± 2 (Ci) vs. 4 ± 1 (S), p=0.04.

Conclusion: It was documented a significant urinary potassium excretion increase in cirrhotic patients on furosemide + spironolactone, only detected by the TTKG.

KEYWORDS: Potassium. Cirrhosis. Transtubular potassium gradient

RESUMEN:

Los cirróticos desarrollan hiperaldosteronismo secundario en estadios avanzados de su enfermedad, requiriendo tratamiento con furosemida + espironolactona. El manejo tubular del potasio (K) en estos pacientes bajo dicho esquema diurético combinado (antagónico) no ha sido aun estudiado, por lo cual decidimos describir el valor de la excreción fraccional (EF) de potasio y del gradiente transtubular de potasio (GTTK) en esta población bajo dichos diuréticos.

Material y Método: Se evaluó prospectivamente la EF de sodio (Na), EFK y GTTK en 18 pacientes (11 hombres), edad promedio 56 años, normokalémicos, cirróticos (Ci) compensados estadios Child Pugh A, B y C, MELD medio 22, portadores de filtrado glomerular, sedimento urinario y ecografía renal normales, tratados con furosemida + espironolactona y dieta hiposódica.

Grupo control: 10 voluntarios sanos bajo igual dieta (S). **Análisis estadístico:** Wilcoxon.

Resultados: Kalemia (mmol/l): 4 ± 0.5 (Ci) vs. 4 ± 0.3 (S), p=NS; EFNa (%): 0.8 ± 0.4 (Ci) vs. 0.5 ± 0.3 (S) p=NS; EFK (%): 9.1 ± 3 (Ci) vs. 10 ± 2 (S), p=NS; GGTK: 6 ± 2 (Ci) vs. 4 ± 1 (S), p=0.04.

Conclusión: Observamos que en cirróticos tratados con furosemida + espironolactona, existe un incremento significativo de la excreción urinaria de potasio, sólo evidenciable por el GTTK.

PALABRAS CLAVE: Potasio. Cirrosis. Gradiente transtubular de potasio.

INTRODUCTION:

Cirrhotic patients develop hyperaldosteronism secondary to advanced stages of their illness and require treatment with furosemide + spironolactone.

The tubular handling of potassium (K) in this patients under such combined diuretic scheme (antagonic) had not yet been studied, therefore we decided to document in an original way the net effect, in this pharmacological context, of the renal potassium handling assessed by means of two specific indicators for that purpose: the fractional excretion of potassium (FEK) and the transtubular potassium gradient (TTKG)¹⁻⁴.

MATERIAL AND METHOD:

The FE of sodium (Na), FEK and TTKG were assessed in 18 patients (11 men), with an average age of 56, normokalemic, suffering from compensated cirrhosis (Ci) stages Child Pugh A, B and C, MELD 22, having normal glomerular filtration, urinary sediment and renal ultrasound, treated with furosemide (average dose: 40 mg/day) + spironolactone (average dose: 100 mg/day) and on hyposodic diet. The control group consisted of 10 healthy volunteers under the same diet (S). For the statistical analysis of the data, the non-parametric test Wilcoxon was applied.

The formulae used were:

- o Fractional excretion of Potassium (K): $FEK = [K \text{ urine} \times \text{serum creatinine} / \text{serum K} \times \text{urinary creatinine}] \times 100$
- o Transtubular Potassium Gradient (K): $TTKG = [\text{urinary osmolality} \times \text{serum creatinine} / \text{serum osmolality} \times \text{urinary creatinine}]$

RESULTS:

Regarding serum potassium value, no significant difference was documented between the studied groups:

Kalemia (mmol/l): 4 ± 0.5 (Cirrhotic) vs 4 ± 0.3 (Healthy), p=NS

There was no significant difference neither in the FENa nor in the FEK, between the studied groups:

FENa (%): 0.8 ± 0.4 (Cirrhotic) vs 0.5 ± 0.3 (Healthy) p=NS;

FEK (%): 9.1 ± 3 (Cirrhotic) vs 10 ± 2 (Healthy), p=NS

Nevertheless, a significant difference was identified in the TTKG between these groups, having a significant higher value in the cirrhotic one:

TTKG: 6 ± 2 (Cirrhotic) vs 4 ± 1 (Healthy), p=0.04.

DISCUSSION

Thick ascending loop of Henle is a segment which is impermeable to water and urea, but permeable to sodium since it has an apical transporter NaK2Cl (which, as indicates its name, cotransports potassium and chloride along with sodium), and whose gradient is given by the existence of a NaKATPase baso-lateral pump. This determines that in this sector a 40% of the sodium filtrated at a glomerular level will be reabsorbed, and that hypotonic urine will be produced, so this is considered to be the sector of the nephron where free water clearance is generated. Therefore, the osmolarity in urine at the end of this segment is around 100 mOsm/l. On the other hand, the same mechanism which contributes to generate the concentration of sodium at a medullar level, and thus, is the driving force of the so called countercurrent mechanism which generates medullar hypertonicity (Figure 1).

Figure 1: nephron sketch with its thick ascending loop of Henle (dark area)

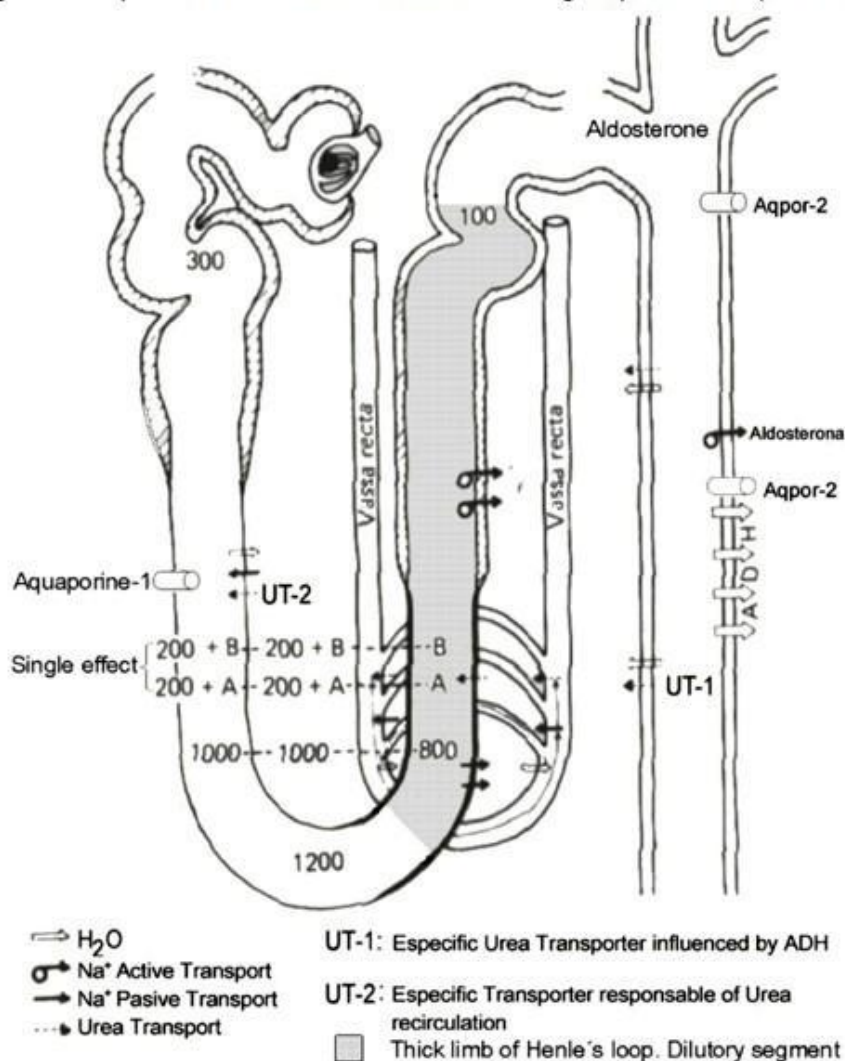


Image authorized by Dr. Juan F. Macías Nuñez

Then, when furosemide blocks the NaK2Cl cotransporter, it induces an increase in sodium excretion, which leads to a state of contraction of volume with the subsequent secondary hyperaldosteronism, which is ultimately the one which ends up producing an increase in the renal excretion of potassium⁴.

The collecting tubule is a segment where approximately a 3-5% of the sodium filtrated is reabsorbed, by means of sodium channels located in the apical pole of the tubular cells; thanks to a concentration gradient generated by a NaKATPase baso-lateral pump. Sodium (cation) reabsorption through the apical cell makes the luminal tubular surface relatively negative in comparison to the intracellular one. Simultaneously, the intracellular potassium is secreted towards the light, through a potassium channel, following an electric and chemical gradient: the electric gradient is based on the luminal electronegativity and the chemical one is based on the high intracellular potassium concentration due to the action of the basolateral pump. All this above mentioned mechanism is intensified in presence of serum aldosterone, which stimulates the increase in number and the function of the sodium and potassium channels as well as the NaKATPase pump of the principal cells, inducing not only higher sodium reabsorption but also a higher secretion of potassium. Spironolactone, an inhibitor which competes with the aldosterone for its receptor, leads to the opposite effect: the loss of sodium and saving of potassium⁵.

The cirrhotic patient in an advanced state usually receives both of the aforementioned drugs (furosemide + spironolactone), which have an antagonistic effect regarding the tubular handling of potassium⁵⁻⁶.

This study documented that in cirrhotic patients on a pharmacological context of furosemide (40 mg/day) + spironolactone (100 mg/day), there was a net increase in the urinary potassium excretion⁶⁻⁸

The fact that the TTKG was more sensitive to detect the increase in potassium excretion in this population could be precisely explained by the fact that TTKG is a better index than the FEK, since this index corrects the phenomenon of the distal handling of potassium related to the one being carried out with water at such level. The water excreted by means of the furosemide dilutes the urinary potassium and underestimates its magnitude of urinary secretion, which the FEK cannot control while TTKG can².

CONCLUSION: It was observed that in cirrhotic patients treated with furosemide + spironolactone, there was a significant urinary potassium excretion, which was only made evident by means of the transtubular potassium gradient.

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In cirrhotic patients sodium retention mechanism and neurohormonal activity are still matter of discussion. Before developing ascitis, cirrhotic patients retain sodium in order to compensate their effective hypovolemia due to the vasodilatation state¹. When cirrhotic patients develop ascitis, they have an increased serum renine, angiotensin II, aldosterone, and noradrenaline levels, phenomenon which explain their sodium retention state despite of their increased serum natriuretic peptide levels².

These patients need a treatment based on diuretics, specially furosemide + spironolactone, being the former able of inducing metabolic encephalopathy³, and hypokalemia.

Even though, renal potassium excretion can be evaluated by measuring urinary potassium concentration, it is already known that TTKG is a better marker for this evaluation. In this sense, Musso et al. showed, in this paper, that TTKG was a better marker than fractional excretion of potassium for detecting an increased urinary potassium excretion in cirrhotic normokalemic patients on furosemide + spironolactone

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This is an original and interesting study since it points out the TTKG, a simple physiological indicator, as a useful marker for evaluating urinary potassium excretion in cirrhotic patients on diuretics.

It would also be useful to evaluate the same potassium urinary excretion markers in cirrhotic patients but at different stages of chronic renal disease, since it is already known that there is a progressive increase in urinary potassium excretion along the chronic reduction of the renal function.

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