RENIN, ALDOSTERONE, URINARY SODIUM AND WEIGHT CHANGE IN CIRRHOTIC PATIENTS WITH ASCITES AND SODIUM RESTRICTION

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SUMMARY

To study the relationship between Plasma Renin Activity (PRA), Plasma Aldosterone Concentration (PAC) and Urinary Sodium Excretion in 24 h volume (UNaV), and to determine the prognostic value of these variables in relation to the response to sodium restriction, we studied 25 patients who had liver cirrhosis and non complicated ascites. A wide variation was found both in basal values and after sodium restriction, in PRA (13.7 ± 15.8 and 13.5 ± 14.7 ng/ml/h) and PAC (377.6 ± 437.5 and 441.1 ± 439.1 pg/ml); UNaV was very low in both occasions (27 ± 33.8 and 16.7 ± 14.2 mmol). A positive correlation between PRA and PAC was found when the sodium intake was in the range of 44 ± 10 mEq/day, but not with severe sodium restriction. No negative correlation was found between PAC and UNaV, suggesting that other factors besides Aldosterone, are important in the sodium retention found in these patients. All patients with an initial high UNaV (> 140 mmol/24 h) have low PRA and PAC and lose weight; the opposite is not true. This study confirms that PAC is not the only factor in the renal sodium handling in cirrhotic patients with ascites, and indicate that UNaV is of prognostic value for the response to dietary sodium restriction.

RESUMO

Renina, Aldosterona, excreção urinária de sódio e variação ponderal em doentes cítricos com ascite e restrição de ingestão de sal

Pretendeu-se estudar, em 25 doentes com cirrose hepática e ascite não complicada, a correlação entre os valores da renina (PRA), aldosterona (PAC) e sódio urinário (UNaV) e determinar o seu valor prognóstico em relação à resposta destes doentes de sódio na dieta. Houve uma grande variação nos valores obtidos em condições basais assim como após a restrição de sódio, quer no PRA (13,7 ± 15,8 e 13,5 ± 14,7 ng/ml/h) quer no PAC (377,6 ± 437,5 e 441,1 ± 439,1 pg/ml), a excreção de sódio urinário foi baixa em ambas as determinações (27 ± 33,8 e 16,7 ± 14,2 mmol). Encontrou-se uma correlação positiva entre PRA e PAC quando a ingestão de sódio era de 44±10mEq/dia, o que não se verificou com a restrição de sódio mais marcada. Não houve correlação negativa entre PAC e UNaV, sugerindo que outros factores além da aldosterona intervêm na retenção de sódio observada nestes doentes. Todos os doentes com uma excreção urinária de sódio inicial alta (30nl/24h), tiveram valores baixos de PRA e PAC e perderam peso; o oposto não é verdadeiro. Este estudo confirma que o PAC não é o único factor no manuseamento renal de sódio em doentes com circrose hepática e ascite, indicando que a excreção urinária de sódio tem valor prognóstico em relação à resposta do doente ascético à restrição de sal na dieta.

INTRODUCTION

Plasma Renin and Aldosterone are said to be increased in cirrhotics with ascites.1,2 Other authors (Wilkinson and Roger Williams, 1980),4 however have shown that PRA and PAC are normal in two thirds of these patients, independent of their positive sodium balance. Most studies show a correlation between PRA, PAC and UNaV in cirrhotic patients with fluid retention.2, 4, 5, 6 On the other hand, in groups of patients with different degree of sodium retention, statistically significant differences were observed in Renin, Aldosterone and Urinary Sodium.8

The present study was undertaken to determine the activation of the Renin-Aldosterone-System (RAS), the relationship between PRA, PAC and UNaV, and their prognostic value for the response to sodium intake restriction in cirrhotics with uncomplicated ascites.

MATERIAL AND METHODS

The study was made in 25 patients with alcoholic liver cirrhosis and ascites, 17 males and 8 females. Criteria for selection of patients were: age under 60; clinical or histological data supporting the diagnosis of alcoholic cirrhosis; ascites; absence of arterial hypertension or renal, cardiac, respiratory or endocrinologic disorders. Laboratorial criteria for inclusion in the study included also a plasma creatinine concentration lower than 97.5 μmols per liter.

The first evaluation was performed after a period of 5 days of bed rest and diet with 44 mEq of sodium daily: a 24 h urine volume was collected for the determination of sodium and creatinine excretion; after 6 hours in supine position fasting blood samples were collected in prechilled tubes with sodium EDTA, centrifuged, aliquoted and stored deep frozen (—20. °C) for the determination of PRA, PAC,
plasma electrolytes and creatinine were obtained too; patients weight was recorded.

A diet containing 22 mEq sodium daily was then started, and the same determinations were made on the 8th day (2nd evaluation). No drugs were given during the study. Two patients were lost to 2nd evaluation because they have been discharged from the hospital before the 7th day.

PRA and PAC were measured by radioimmunoassay (Angiotensin I radioimmunoassay Kit — Cis sorin) — Aldosterone radioimmunoassay Kit — Cis sorin). Normal values in our laboratory for subjects at rest in supine position are: PRA = 0.24-3.24 ng/ml/h; PAC = 12-125 pg/ml. All values were measured twice. The coefficient of variation in within — assay and between — assay for PRA and PAC were respectively 5.8-7.5%, 9.8-12.2% for PRA, 7.3-8.2% 11.0-13.1% for PAC.

Urinary sodium excretion (24h urine) was measured by ion selective method (Astra Beckman), with normal value: 100-260 mmol/24h.

RESULTS

On the first evaluation (Fig. 1), mean PRA was 13.7 ± 15.8 ng/ml/h (range 0.1 to 62.6 ng/ml/h); the levels were normal (< 3.24 ng/ml/h) in 8 patients and elevated above the normal range in 17 patients. Mean PAC was 377.6 ± 437.5 pg/ml (range 45 to 2100 pg/ml); the levels were normal (< 125 pg/ml) in 5 patients and elevated in 20 patients. Mean UNaV was 27 ± 33.8 mmol/24 h (range 1 to 140 mmol/24 h) have shown very low levels of urinary sodium excretion.

On the 2nd evaluation (Fig. 1), mean PRA was 13.5 ± 14.7 ng/ml/h (range 0.1 to 54.3 ng/ml/h); the levels were normal (<3,24ng/ml/h) in 6 patients and elevated in 17 patients. Mean PAC was 441.1 ± 439.1 pg/ml (range 43 to 1990 pg/ml); The levels were normal (< 125 pg/ml) in 4 patients and elevated in 19 patients. Mean UNaV was 16.7 ± 14.2 mmol/24 h (range 2 to 51 mmol/24 h).

Between the 1st and 2nd evaluation 11 patients put on weight (mean: 827.2 g) and 14 patients lost weight (mean: 1317 g).

PRA was found to be directly related to PAC (Fig. 2), at the first evaluation (r: 0.45, p < 0.05); no correlation was found at the 2nd evaluation (r: 0.39, p > 0.05). But there was no significant difference between the two evaluations in relation to the mean values of PRA and PAC.

On both evaluations a negative correlation was found between PRA and UNaV (1st = r: -0.41, p > 0.05/2nd = r: -0.54, p < 0.01) but not between PAC and UNaV (1st = r: -0.31, p > 0.05/2nd = r: -0.28, p > 0.05).

According to Fig. 1, there is an increased number of patients below 6 ng/ml/h of PRA, 400 pg/ml of PAC, 30 mmol/24 h of UNaV, and a widespread dispersion above those values. These data make possible to draw a line at the above mentioned values.

In relation to the 1st evaluation there are the following further observations (Table 1): all patients with high PRA (>6 ng/ml/h) and/or high PAC (> 400 pg/ml) had UNaV < 30 mmol/24 h but no correlation was found between these values of PRA and UNaV (r: - 0.02,
p > 0.05), or PAC and UNaV (r: 0.29, p > 0.05); these patients have a variable weight change.

All patients with UNaV < 30 mmol/24 h, have unpredictable weight change without relation with the values of PRA or PAC, which are very variable, but all with UNaV > 30 mmol/24 h have low PRA and low PAC and have lost weight. There was no changes on plasma Na+ levels from the first to second evaluation, neither correlation with PAC or PRA.

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\text{Figure 2: Relationships between PRA and PAC on both evaluations. On the 1st, a positive correlation was found (r: 0.39, p > 0.05).}
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\text{on the 2nd, no correlation was found (r: 0.39, p > 0.05).}
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\text{TABLE 1 On the 1st evaluation, all patients with high PRA and/or high PAC had low UNaV; all patients with high UNaV have lost weight}
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<table>
<thead>
<tr>
<th>PRA</th>
<th>PAC</th>
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<tr>
<td>&gt; 400</td>
<td>&lt; 400</td>
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<tr>
<td>12</td>
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DISCUSSION

The results of the present study confirm that PRA and PAC are quite frequently elevated in cirrhotics with ascites.\(^1\) \(^2\) \(^3\) In spite of this, some authors found normal values of these variables in two thirds of these patients,\(^4\) \(^5\) showing a nonstimulated RAS. These different findings lend support to the two most accepted theories about ascites formation:\(^4\) \(^5\) \(^6\) traditional v.s. over-flow theory. The first theory supports that a sequestration of fluid in the splanchnic territory with reduced effective plasma volume would be the most important signal for activation of RAS with the consequent sodium retention and ascites formation.\(^4\) However some studies show that no correlation can be established between PRA and renal plasma flow (or effective renal plasma flow) or glomerular filtration rate.\(^2\) The second theory, proposed by Lieberman,\(^3\) \(^4\) \(^9\) supports that in other cases the primary event is excessive sodium retention by the kidneys, with a resultant expansion of plasma volume. These patients have a normal PRA and PAC, they might have either a deficiency of natriuretic factor or an increased renal tubular sensitivity to aldosterone; probably both concepts are true, according to the patients. It seems that several factors may stimulate renin secretion in patients with cirrhosis and ascites: intrarenal redistribution of blood flow,\(^4\) \(^6\) hypotenaemia,\(^4\) alterations in splanchnic haemodynamics,\(^2\) humoral agents produced by the liver,\(^2\) neurogenic splanchno-renal reflex.\(^2\) When there is a normal PAC most authors evoke mechanisms other than aldosterone to explain sodium retention, like failure of the natriuretic factor\(^9\) \(^11\) \(^12\) or alterations in the proximal reabsorption of sodium with decreased distal delivery of filtrated and reduced free water excretion.\(^1\) \(^11\)

We could not confirm early observations\(^2\) \(^5\) of positive correlation between PRA and UNaV, but not between PAC and UNaV. These findings were described in several studies;\(^1\) \(^9\) \(^10\) the relation PRA-UNaV may be explained by decrease delivery of sodium to the distal tubule, a strong stimulus to renin production via the macula densa.\(^10\) The absence of relationship PAC-UNaV in our study demonstrates the interference of other factors besides PAC on renal sodium handled in cirrhotic patients with ascites. There is some evidence\(^1\) of a more important sodium reabsorption in the proximal than distal tubule, this may play a fundamental role in pathogenesis of sodium retention in these patients with normal or low PAC.

More than the plasma values of both hormones, urinary sodium excretion appears as the only factor with prognostic value in relation to the response to a sodium restriction diet. As a matter of fact, all patients with UNaV > 30 mmol/24 h lost weight, independantly of their initial values of PRA or PAC; patients with UNaV < 30 mmol/24 h can have unpredictable behaviours, either respond to sodium restriction or not, independantly of their PRA and PAC values. So urinary sodium excretion is an important (and easy) measurement in these patients because it is an important prognostic marker in relation to the response to sodium restriction diet. Probably those with high sodium excretion will be the patients with better homeostatic mechanism and so better survival rates as shown previously by Rodés and al.\(^6\)
REFERENCES


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