CORRELATION BETWEEN PLASMA SODIUM ACETATE CONCENTRATION AND SYSTEMIC VASCULAR RESISTANCES

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Summary

Acetate in dialysis fluid induces during haemodialysis a fall in systemic vascular resistance. In patients with hepatic insufficiency, acetate concentrations are higher than in patients without hepatic insufficiency and in such patients vascular sensitivity to acetate is perhaps potentiated by modifications of acid base status. The close inverse correlations between acetate concentrations and systemic vascular resistance are strong indications that acetate is a major factor involved in the genesis of 'dialysis hypotension'.

Introduction

In 1964 Mion et al [1] proposed sodium acetate as an alternative to bicarbonate as the buffer in dialysate fluid because it increases solubility of the calcium and magnesium salts. Since then many cases of 'acetate intolerance' have been reported [2]. During haemodialysis (HD), acetate is considered responsible for cardiovascular instability [3,4] and the development of arterial hypoxaemia [5].

The effect of acetate on the cardiovascular system remains a controversial subject. We have undertaken this study to determine how sodium acetate modifies haemodynamic parameters, particularly systemic vascular resistance (SVR), in regard to plasma acetate (P Na A).

Patient selection and methods

In 17 adult chronic haemodialysis patients, the plasma sodium acetate concentration and the haemodynamic modifications were studied during a single HD treatment. The patients mean age was 45 ± 4 years. The mean blood pressure was 123 ± 13mmHg, mean diastolic pressure 92 ± 12mmHg. The observed hypertension was due to fluid overload. They had no symptoms of heart failure, mean cardiac index was 3.64 ± 0.48 L.min⁻¹.m⁻², mean pulmonary wedge pressure was 16 ± 6mmHg.
Thirteen patients have no hepatic insufficiency, mean age: 47 ± 3 years, treated by HD for 22 ± 7 months. Four patients have hepatic insufficiency, mean age: 43 ± 5 years, treated by HD since 18 ± 10 months.

All patients were dialysed for 6 hours twice weekly and their haematocrit, blood urea nitrogen, creatinine and electrolytes were comparable. All patients were treated with a 1.4 m² dialysar (Cordis Dow C 4000) for a 330 minutes single pass HD. The heparinisation was performed at a rate of 1332 IU/hour. The composition of the dialysate was: Na⁺ 138mEq/L, K⁺ 2mEq/L, Ca²⁺ 3.5mEq/L, Mg 1.5mEq/L, Acetate 38mEq/L, and Cl⁻ 107mEq/L.

The plasma sodium acetate titration was performed by isotachophoresis. Each titration was performed twice on 5μl plasma from a peripheral vein. In each patient, P Na A was determined before, each 30 minutes during and 30 minutes after HD.

The haemodynamic parameters monitored before, during each 30 minutes and 30 minutes after the end of the HD were: blood pressure (BP) by oscilometry (Dynamap); pulmonary arterial and wedge pressure (PAP and PWP) were measured by a Swan-Ganz catheter; heart rate (HR) derived from the ECG; cardiac index (CI) was determined by thermodilution; systemic vascular resistances (SVR) and the stroke index (SI) were calculated as usual; weight loss was monitored by means of a bed scale.

Statistics were performed by the paired Student's 't' test. The arterial gases, arterial oxygen tension (PaO₂), carbon dioxide (PaCO₂), pH and bicarbonate (HCO₃⁻) were measured simultaneously with P Na A.

Results

Plasma Na acetate level

Before treatment no acetate can be detected in the patient's blood. During the first 30 minutes of dialysis P Na A increases similarly both in the patients with and without hepatic insufficiency. After 30 minutes P Na A behaves differently in these two types of patients. In the patients without hepatic insufficiency, we observe a slow increase of P Na A until 180 minutes when P Na A reaches a peak of 2.70 ± 0.2mEq/L then tends to plateau and decreases from 300 minutes.

In the patients with hepatic insufficiency the increase of P Na A continues until the end of treatment. The maximum of P Na A is reached at 330 minutes at 3.30 ± 0.3mEq/L (Figures 1a and 1b). These patients have a significantly higher plasma acetate than patients without hepatic insufficiency (p<0.01).

Modifications of blood pressure

Whatever the initial value BP decreases in all patients during haemodialysis. In the patients without hepatic insufficiency the maximum decrease is observed at 180 minutes, then mean BP remains stable. The fluid removal was 3125 ± 613ml (mean ± SD). In the patients with hepatic insufficiency BP decreases during the whole course of haemodialysis with a fluid removal of 1930 ± 420ml (mean ± SD). The decrease of BP is more marked in these patients than in the
Figure 1a. Plasma Na acetate level, blood pressure and systemic vascular resistances evolution during haemodialysis (n = 13)

Figure 1b. Plasma Na acetate level blood pressure and systemic vascular resistances evolution in 4 chronic haemodialysis patients with hepatic insufficiency
Figure 2a. Relationship between $\Delta$SVR and plasma Na acetate level in 13 chronic haemodialysis patients during haemodialysis

$n = 164$
$r = -0.829$
$y = -344x + 388$
$\alpha < 0.001$

Figure 2b. Relationship between $\Delta$SVR and plasma Na acetate level in 4 chronic haemodialysis patients with hepatic insufficiency

$n = 35$
$r = 0.892$
$y = -350x + 324$
$\alpha < 0.001$
patients without hepatic insufficiency (p<0.01). Two severe symptomatic hypotensive episodes occurred in the hepatic group, whereas only one case of severe hypotension was observed in the non hepatic group and in this case we can imply an excessive removal of fluid.

**Effect of P Na A on the SVR**

Figures 1a and b display the variations of SVR with respect to variation of P Na A. In the non hepatic patient a maximum decrease of SVR to 721 ± 197 dyn.sec.cm\(^{-5}\) (p<0.001) at 180 minutes occurs with a maximum increase of P Na A; then SVR increases towards the initial value as P Na A decreases. In the hepatic patients SVR decreases until the end of treatment to 703 ± 103 dyn.sec.cm\(^{-5}\). This decrease of SVR occurs inversely to the increase of P Na A.

If we plot the SVR against the P Na A of each patient in each group (Figures 2a and 2b), we see that there is a close inverse relationship between P Na A and SVR. These relationships can be described in terms of a regression function y = -344 x + 369 in non hepatic and y = -350 x + 324 in hepatic patients. These equations can be rearranged to the more meaningful form y = -344 (x -1.07) in group I and y = -350 (x -0.92) in group II, which describes the lines in terms of intercept on the abscissa instead of the ordinate. The values so obtained, 1.07mEq/L and 0.92mEq/L indicate the level of P Na A at which we can expect SVR to decrease and thus provide a measure of the threshold. The values -344 and -350 indicate the slope of the regression line and thereby reflect the sensitivity or gain of the response (Table I).

<table>
<thead>
<tr>
<th>TABLE I. Threshold level and sensitivity of the plasma level response curve in groups I and II</th>
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<tbody>
<tr>
<td>Threshold of P Na A</td>
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<tr>
<td>---------------------</td>
</tr>
<tr>
<td>Group I</td>
</tr>
<tr>
<td>Group II</td>
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* p<0.01

Patients with chronic hepatic insufficiency show a lower threshold level than non hepatic patients

**Effect of P Na A on CI**

In each group of patients we have an increase in CI during the course of HD. In non hepatic patients CI increases from 3.98 1.min\(^{-1}\).m\(^{-2}\) ± 0.45 to 4.50 1.min\(^{-1}\).m\(^{-2}\) ± 0.47 (p<0.05) and in hepatic patients CI increases from 3.27 1.min\(^{-1}\).m\(^{-2}\) ± 0.57 to 4.88 1.min\(^{-1}\).m\(^{-2}\) ± 0.61 (p<0.001).

This increase of CI seems to be related to the increase of P Na A and is observed despite the fluid removal and the decrease of filling pressure (PWP). The increase in CI is due to an increase of heart rate more than an increase of SI (Table II). This increase of HR is a well known secondary effect of vasodilator drugs.
TABLE II. Variations of CI, HR and SI in each group during HD

<table>
<thead>
<tr>
<th></th>
<th>CI 1.min⁻¹.m⁻²</th>
<th>HR b.min⁻¹</th>
<th>SI 1.min⁻¹.m⁻²</th>
<th>PWP mmHg</th>
</tr>
</thead>
<tbody>
<tr>
<td>non hepatic</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>before HD</td>
<td>3.98 ± 0.45</td>
<td>78 ± 12</td>
<td>50.92 ± 7.49</td>
<td>17 ± 4</td>
</tr>
<tr>
<td>after HD</td>
<td>4.50 ± 0.47*</td>
<td>98 ± 9**</td>
<td>45.36 ± 4.99</td>
<td>7 ± 3</td>
</tr>
<tr>
<td>hepatic</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>before HD</td>
<td>3.27 ± 0.57</td>
<td>81 ± 8</td>
<td>45.73 ± 5.18</td>
<td>15 ± 4</td>
</tr>
<tr>
<td>after HD</td>
<td>4.88 ± 0.61***</td>
<td>100 ± 7***</td>
<td>49.21 ± 7.63</td>
<td>8 ± 3</td>
</tr>
</tbody>
</table>

* p<0.05    ** p<0.01    *** p<0.001

Effects of P Na A on acid-base status

Following the increase in P Na A, HCO⁻³ increases in all patients (Figures 3a and 3b).

In non hepatic patients HCO⁻³ increases until 180 minutes then tends to plateau, whereas in patients with hepatic insufficiency HCO⁻³ increases until the end of treatment but in a less marked way.

During HD we see reduction in arterial oxygen tension. This is more marked in hepatic patients. pH changes in a similar way in all patients with no statistical difference between hepatic and non hepatic patients.

Discussion

The P Na A levels found with isotachophoresis are lower than those reported by Tolchin et al [6] and Mansell et al [7] using a gas liquid chromatography method. In the patients with hepatic insufficiency we have found higher P Na A concentrations than in patients without hepatic insufficiency. We suggest, as did Mansell et al [7], that this increase in these patients is due to a diminished metabolic capacity for acetate. This has been reported previously in hepatectomised animals by Harper et al [8]. The vasodilator effect of acetate has been known since 1928 [9] and our study shows that the increasing P Na A seems to be responsible for the decrease in SVR as shown by the close relationship between ΔSVR and P Na A. Aizawa [10] found similar results after acetate infusions in chronic haemodialysis patients. Thus Na-Acetate can be one of the factors among others which can produce vascular instability and 'dialysis hypotension'. The other possibly important factors are fluid removal, Na balance and inadequacy of heart function.

Simultaneously with the decrease in SVR we found an increase in CI. This increase is secondary to the increase in HR rather than to the increase in SI. It can be interpreted as a compensatory mechanism to the vasodilator effect of acetate. Whereas Na acetate can produce in these patients, without myocardial insufficiency, a deleterious effect, we have shown [11] that this vasodilator
Figure 3a. Plasma Na acetate level, PWP and CI evolution in 4 chronic haemodialysis patients with hepatic insufficiency

Figure 3b. Plasma Na acetate level, PWP and CI evolution during haemodialysis in chronic haemodialysis patients (n = 13)
effect can be of value in patients with acute pulmonary oedema or heart failure. In these patients [11] we observed that the increase of CI was due more to an increase of SI than to an increase of heart rate. Thus Na acetate has a similar action to nitrates at high doses.

The hypoxaemia found during HD is reported to be due to the increase in plasma sodium acetate [5]. In our study we found that the fall in arterial oxygen tension is more marked in hepatic patients. However how acetate can induce this hypoxaemia is still to be elucidated.

The correlation between ΔSVR and P Na Acetate in hepatic and non hepatic patients is a strong argument that acetate can play an important role in the genesis of ‘dialysis hypotension’. In the patients presented in this study those with a higher acetate concentration have a greater vascular instability. The question remains open whether acetate has a different effect on vascular smooth muscle in hepatic patients than in non hepatic patients as shown by the differences in threshold of acetate seen. Perhaps the differences in the acid base status mentioned in hepatic and non hepatic patients may be one explanation of the differences in threshold noted.

Conclusion

Na acetate in dialysate fluid induces a decrease of SVR during HD. A close correlation can be established between the increase of P Na A and the decrease of SVR.

The patients with hepatic insufficiency in dialysis conditions display higher acetate concentrations than non hepatic patients and they seem to have a greater vascular sensitivity to acetate vasodilator effect. This effect of Na-Acetate can be one of the factors inducing ‘dialysis hypotension’ in some patients.

During acetate dialysis an increase of CI is noticed, due, in patients without myocardial insufficiency, to an increase in heart rate.

Acknowledgments

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References

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Open Discussion

BERGSTRÖM (Stockholm) What was your dialysate sodium concentration?

SCHOHN 138mm/L.

BERGSTRÖM So you might have had some shifts of sodium as well?

SCHOHN Yes, it’s possible.

BERGSTRÖM I ask you because I agree that the cause of hypertension during dialysis is multifactorial and that acetate is one of the factors involved, but I think that this should be looked upon in relation to sodium shifts. We showed some years ago that acetate, at high sodium concentration, had no significant effect on blood pressure in our patients, but when we had a low sodium concentration (133) in the dialysate we saw a difference between acetate and bicarbonate dialysis so that the acetate had more of a blood pressure lowering effect. It was not a significant difference but it was a little difference.

SCHOHN We have not analysed this effect.

HAMPL (Berlin) Please give me some data on the initial cardiac condition of your patients because patients behave differently under treatment if the cardiac initial condition is different. I mean, patients with cardiac insufficiency or patients without cardiac insufficiency, because the behaviour of the stroke volume and the peripheral resistance must be very different.

SCHOHN None of our patients show clinical features of heart failure and as Dr Wehle said in the previous communication, we think that the increase of cardiac index is a compensatory mechanism.

HAMPL I’m afraid that you have in this situation patients without cardiac insufficiency, because if we take off a lot of volume the cardiac condition will be better and the cardiac index will be higher.

ELIAHOU (Tel Aviv) I would like to support this because I think that you cannot get beyond this Starling curve in dialysis patients. The removal of overload, even though without heart failure, can improve the inotropic effect. There’s another factor which has to be studied also, the calcium in the serum, which is always improved after dialysis, so I want to ask if you have paid attention to that.

SCHOHN We are aware of the problems induced by fluid removal on cardiac function curves. But as you have seen the left ventricular filling pressure decreased and nevertheless cardiac index increased so we believe that Na acetate participates in the increase of cardiac index. Kirkendohl has shown experimentally an increase of cardiac index after Na acetate.