THE INFLUENCE OF ACETATE VERSUS BICARBONATE ON PATIENT SYMPTOMATOLOGY DURING DIALYSIS

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Summary

The effect of large-surface area dialysis (LS) using dialysate containing both acetate and bicarbonate (LS–C) on a patient’s symptomatology was compared with that noted with acetate (LS–A) or bicarbonate (LS–B) in the dialysis fluid. Patients experienced significantly more symptoms and deterioration of objective performance test scores with both LS–A and LS–C than LS–B. Furthermore, a correlation was seen between plasma acetate level at the end of dialysis and decrement in the performance test scores. The results suggest that accumulation of acetate rather than acute alteration in acid-base status is primarily responsible for the morbidity.

Introduction

We previously reported that dialysis-induced morbidity was reduced by substituting bicarbonate for acetate in the dialysate [1]. Patients who became symptomatic with acetate dialysis typically showed a fall in blood bicarbonate level during dialysis, suggesting that these patients had difficulty in converting acetate to bicarbonate effectively.

These original studies did not clarify the question of whether the elevations in blood acetate per se or the secondary changes in acid-base balance or both were responsible for the morbidity associated with acetate dialysis. It was the purpose of the present study to clarify this point.

Patients and Methods

Patients were selected at random among stable chronic dialysis patients at the Dialysis Research Facility of the University of Washington. Nine patients completed the study. Five were males and 4 were females; their ages ranged from 41 to 74. The C–DAK 2.5 m² (Cordis-Dow Model V) dialyser was chosen because of its high transfer rate for acetate and bicarbonate. Treatment protocols were
classified into three types depending on the dialysate acetate and bicarbonate composition:

1 LS—A containing 38 mEq/L of acetate
2 LS—B containing 35 mEq/L of bicarbonate
3 LS—C containing 38 mEq/L of acetate plus 10 mEq/L of bicarbonate.

The LS—C protocol was designed to give the same acetate load as the LS—A protocol, while preventing fall of blood bicarbonate levels in patients intolerant to acetate. A pilot study indicated that 10 mEq/L of bicarbonate is sufficient for this purpose. The other composition of dialysate was 140 mEq/L of Na, 3.5 mEq/L of calcium, 102 mEq/L of chloride, and 35 mg/dl of urea. Potassium concentration was adjusted to the patient’s requirement. Dialysate was supplied by Bi-ProR (BD-Drake Willock) dialysate proportioning machine especially designed to produce bicarbonate dialysate.

Each patient received 5 treatments with each type of dialysate for a total of 15 dialyses. The order of the runs was randomly assigned. Patients were not informed of the type of treatment. Dialyses were carried out for 4 hr with blood flow rate of 200 ml/min and dialysate flow of 500 ml/min. Negative pressure was adjusted as needed for the patient and infusion of saline was started whenever it was necessary to avoid serious hypotension. After dialysis, the patient was interviewed for the symptoms. Each symptom was scored into three grades: 1 for no symptoms, 2 for moderate symptoms, and 3 for severe symptoms. The average value for each symptom for the 5 dialyses of each type was used for statistical analysis.

The Continuous Performance Test (CPT) and Choice Response Time Test (CRT) were performed by each patient before and after each treatment in order to provide objective evaluation of the patient’s well-being [2]. The CPT measures percentage of correct response of a patient to identify a letter ‘x’ among other letters projected on a screen alternately in a randomised fashion. The CRT measures the response time needed to identify a colour among three different colours projected on a screen in randomised fashion. The results are expressed in milliseconds. Both tests were scored as pre-dialysis values minus post-dialysis values. Hence, larger scores reflected greater deterioration in performance (see Table I).

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<th>TABLE I. Deterioration in Performance Scores</th>
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* Differs from LS—B at p<0.025

Blood gases were measured hourly. All the blood samples were handled anaerobically and measured promptly with an IL—113 blood gas assembly. Blood bicarbonate levels were calculated from pH and pCO2, using the Henderson—
Hasselbalch equation. Plasma acetate levels were measured by an enzymatic method [3].

Results

Plasma Acetate and Bicarbonate

The results are shown in Figures 1 and 2. The plasma acetate levels in both LS−A and LS−C protocols were essentially the same, being characterised by a rapid rise at one hr, followed by a gradual increment toward the end of the dialysis. With the LS−B technique, plasma acetate was assumed to be zero. There was almost no increment in blood bicarbonate in LS−A, while in LS−B and LS−C there was a significant increment of the levels toward the end of dialysis. Behaviour of

Figure 1. Changes in plasma acetate during LS−A (□) and LS−C (Δ) dialysis. Average values ± 1 S.E. for 9 patients
Figure 2. Changes in plasma bicarbonate during LS–A (□), LS–B (○) and LS–C (△) dialysis. Average values ± 1 S.E. for 9 patients.

overall blood bicarbonate levels in LS–C was almost similar to that of LS–B. These results indicate that the primary goals of the study described in the section on Patients and Methods were achieved reasonably well.

*pCO₂ and pH*

The pCO₂ change in general was relatively small (37 → 34). The average difference of the levels between the protocols was not significant at any time. A statistically significant fall in pCO₂ was seen at 4 hr in LS–A and LS–C (p < 0.05). There was a universal elevation in blood pH in all treatments (7.40 → 7.52 with LS–C). The change was significantly less in LS–A than in LS–B or LS–C. Furthermore, pH rose slightly more with LS–C than with LS–B (a defect of our protocol), although the difference between these two values was not statistically significant.
**Symptom Scores**

The scores are expressed as mean severity of each symptom. Symptoms rated by patients as significantly more severe after LS-A and LS-C than after LS-B included *nausea* (LS-A p < 0.04; LS-C p <0.007 when compared to LS-B), *headache* (LS-A p <0.03; LS-C p<0.026), *postdialysis fatigue* (LS-A p <0.035; LS-C p <0.03), and *dizziness* (LS-A p <0.035, LS-C p <0.009). Neither disorientation, vomiting, or any other symptoms showed statistically significant differences between LS-A or LS-C and LS-B.

**Performance Tests**

The values (Table I) are the absolute values of average pre-post difference scores, measured in milliseconds for the CRT and percent correct for the CPT. Larger absolute numbers indicate greater performance deteriorations. CRT performance was significantly worse after LS-A and LS-C runs when compared with LS-B. Deterioration of CPT after LS-C was significant when compared with LS-B (p <0.06), and that after LS-A also approached significance.

**Other Results**

Plasma acetate levels at 4 hr correlated significantly with the CRT values (r = -.83, p <0.01), but not with the CPT, suggesting that CRT was the most sensitive single criterion for the assessment of the patient’s morbidity.

**Discussion**

A beneficial effect on patient morbidity of the use of bicarbonate instead of acetate for clinical dialysis in selected patients has been reported previously [1]. The present study was designed to determine whether acetate intolerance or secondary acid-base effects were primarily responsible for this morbidity. In the present study, the loss of bicarbonate was successfully prevented by using an acetate-bicarbonate combination dialysate bath containing 38 mEq/L of acetate and 10 mEq/L of bicarbonate. The results support the hypothesis that it is the presence of acetate, and not the secondary effects on acid-base balance, that contributes to the occurrence of symptoms observed during LS-A. Furthermore, a statistically significant correlation was seen between the CRT score and plasma acetate level, indicating that patients who could not metabolise acetate fast enough also tended to have more serious morbidity.

In the present study there was a less striking difference in symptoms and performance between LS-A and LS-B than noted previously [1]. Also, in the present study plasma bicarbonate failed to drop during LS-A dialysis as it did in the earlier study [1]. These differences presumably are due to the fact that in the earlier study only symptomatic (acetate-intolerant) patients were included, whereas in the present study patients were picked at random.
Acknowledgments

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References


Open Discussion

AVRAM (Brooklyn, N.Y.) Can you predict a change in the long range lipid metabolism of patients on dialysis?

NAGAI We have not yet studied that.

CAMBI (Parma) According to the literature the toxic effects of acetate increase with the serum levels of acetate. Actually you claim that these physiological amounts of acetate are toxic. In the literature it is underlined that among the effects on vascular stability of acetate, the effect on pulse rate and peripheral resistance are more important than the effect on cardiac output. I don't understand how it is possible to describe this combination of symptoms that are regarded as those of vascular instability generally speaking, if the amount of acetate is not at intolerable levels.

NAGAI With regard to the vascular instability in both acetate dialysis and bicarbonate dialysis, the incidence of hypotension was equal and we assume that this would be due to the fact that we use 140 mEq/litre of sodium concentrate instead of the lower sodium concentrate and according to Bergström, if we use higher sodium concentrations the vascular instability is minimal.

PORT (Ann Arbor) I was wondering if you have compared the symptoms that you observed and the post dialysis serum acetate concentrations.

NAGAI Yes, we tried to correlate the blood acetate levels and the occurrence of symptoms. We did see some trend, that when the patients' acetate levels were higher the patients seemed to have more symptoms, but the number of patients we have studied were not so many that we could positively say that there is a correlation between them. But my impression is that when the blood acetate level is higher, the patients are more symptomatic.

DE BASTIANI (Ferrara) What kind of test of performance or continuous performance, and what kind of mental test was used, and what kind of statistical analysis?
NAGAI  The response time test which is a psychological test taken care of by the technicians, and a continuous performance test where the patient has to perform different assigned tasks after identifying the correct signal.

DE BASTIANI  And for statistical analysis you used what type of test? I don’t understand.

NAGAI  Each of the tests was done before and after dialysis, and if there was deterioration of the performances that means that pre-dialysis values were better than the post dialysis values, and thus if we subtracted the post values, there was negative value, but we disregarded those negative values. So if the numbers are bigger that means that the deterioration of the performance was worse.

HAMPEL (Berlin)  Have you checked all your measurements in relationship to the ‘dry weight’ of the patient?

NAGAI  There was a significant correlation between the blood acetate levels and the patient’s dry weight and also the performance test and the blood acetate levels. Would that be enough?

HAMPEL  No, I think it is not enough, because by exceeding a certain ultrafiltration rate you have a subsequent critical decrease in plasma volume and then you have diminished tissue perfusion which is followed by acidosis. By disturbance in peripheral vasoconstriction (as in conventional haemodialysis) a further deterioration of the tissue perfusion with hypoxia followed by hyperventilation with a drop in pCO2 must result. This can ultimately bring about a dangerous acidosis, induced bradycardia and severe hypotension.

NAGAI  We have not decided anything in that way.

HAMPEL  It is very important.