

ACID-BASE AND ELECTROLYTE TEACHING CASE

Metabolic and Hemodynamic Advantages of an Acetate-Free Citrate Dialysate in a Uremic Case of Congenital Methylmalonic Acidemia

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INDEX WORDS: Methylmalonic acidemia; acetate dialysate; citrate dialysate.

Methylmalonic acidemia (MMA) is an organic acidemia in the class of diseases caused by enzymatic defects in the catabolism of branched-chain amino acids (valine, isoleucine, methionine, and threonine), odd-chain fatty acids, and cholesterol. MMA is an autosomal recessive disorder caused by a deficiency in methylmalonyl-coenzyme A (CoA) mutase (encoded by the *MUT* gene) or ATP:cob(I)alamin adenosyltransferase activity (encoded by the *MMAB* gene).¹ The causes of MMA are heterogeneous, but the clinical presentation of patients is similar. Affected infants present with recurrent vomiting, respiratory distress, lethargy, and severe ketoacidosis, which may progress rapidly to coma and death if not treated aggressively.² Hypoglycemia, hyperglycemia, and hyperammonemia may also occur.

Because most children now survive the acute metabolic crisis, long-term complications have become more relevant. Increased levels of organic acids, including methylmalonic acid, can be cytotoxic, with effects on cells in the central nervous system, bone marrow, and kidneys.^{3,4} Kidney diseases occur as particular complications of MMA; the most common is tubulointerstitial nephritis.⁵⁻⁷ Similar kidney diseases do not occur with other organic acidemias, including

propionic aciduria, which is caused by a deficiency in the enzyme before methylmalonyl-CoA mutase in the same catabolic pathway. The pathophysiological basis of kidney disease in patients with MMA is unclear; however, the damage to the kidney is irreversible and hemodialysis (HD) or continuous ambulatory peritoneal dialysis may be needed for end-stage renal disease.⁸ Kidney or liver transplantation is an alternative option,^{9,10} but experience with transplantation for this condition is limited.¹¹

In Japan, the majority of HD patients currently are treated with an acetate-containing bicarbonate HD solution (acetate dialysate) with a concentration of 48 to 60 mg/dL (8 to 10 mmol/L). Acetate may induce the production of cytokines and dilatation of vessels,^{12,13} but a small amount of acetate is necessary to maintain the pH of the HD solution at 7.1 to 7.6 to prevent precipitation of calcium and magnesium.¹⁴ Although patients with acetate intolerance normally need acetate-free biofiltration, the standard dialysate still includes acetate. Recently, Ahmad et al¹⁵ reported that a dialysate containing citrate instead of acetate was well tolerated and allowed an increased dialysis dose. Acetate-free citrate HD solution (citrate dialysate) is available as Carbostar (Ajinomoto Corp, Tokyo, Japan) in Japan. Here, we report the case of a patient with end-stage renal disease caused by MMA in whom we evaluated HD treatment with citrate or acetate dialysate.

CASE REPORT

Clinical History and Initial Laboratory Data

A 26-year-old woman was admitted to the emergency department of Jichi Medical University Hospital, Shimotuke, Tochigi, Japan, on October 10, 2007, with fever, cough, and vomiting that had persisted for several days. She was the second child born to nonconsanguineous parents after a full-term normal pregnancy, and her elder sister did not have medical problems. At age 1 month, her growth had been slightly delayed because of weak breastfeeding, and at

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Received November 6, 2008. Accepted in revised form April 28, 2009. Originally published online as doi: 10.1053/j.ajkd.2009.04.033 on July 6, 2009.

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0272-6386/09/5404-0022\$36.00/0
doi:10.1053/j.ajkd.2009.04.033

3 months, she was vomiting 1 to 2 times daily. MMA was diagnosed at 6 months of age, but genetic analysis was not performed. During infancy, she received vitamin B₁₂ therapy, but her symptoms did not improve. At 2 years of age, she had a severe acidosis episode that resulted in spastic leg paralysis. Subsequently, she had intermittent acidosis episodes. At 12 years of age, serum urea nitrogen (SUN) and serum creatinine levels were 7 mg/dL (2.5 mmol/L) and 1.0 mg/dL (88 μ mol/L), respectively. Her kidney function then gradually deteriorated. At a regular medical checkup in August 2007, SUN and serum creatinine levels were 56 mg/dL (20.0 mmol/L) and 4.7 mg/dL (415 μ mol/L), respectively. Estimated glomerular filtration rate was 10.5 mL/min/1.73 m² (0.18 mL/s/1.73 m²).

At hospitalization, SUN and serum creatinine levels were 64 mg/dL (22.8 mmol/L) and 6.04 mg/dL (534 μ mol/L), respectively. Acute-on-chronic renal failure was diagnosed that probably was precipitated by acute bronchitis and dehydration. After admission, the patient was treated with intravenous infusion and injection of furosemide in addition to antibiotics. On October 15, SUN and serum creatinine levels were increased to 74 mg/dL (26.4 mmol/L) and 7.26 mg/dL (642 μ mol/L), respectively.

HD was initiated for 3 hours 3 times each week, and nausea and vomiting disappeared gradually. HD first was performed using an acetate-containing bicarbonate dialysate (AK Solita DP; Ajinomoto Corp), but the patient's blood pressure (BP) was unstable during these sessions and she sometimes reported systemic flushing when she had acute hypotension. In patients with MMA, there is a tendency for methylmalonic, methylcitric, propionic, and acetic acids to accumulate in serum because of enzymatic deficiencies, and we were concerned about an overload of acetic acid with use of the acetate-containing dialysate. Therefore, she was switched to HD with a citrate dialysate (Carbostar). This led to a dramatic decrease in acute hypotension, and she became asymptomatic during HD. Based on this observation, we studied the changes in hemodynamic and laboratory data associated with the switch from acetate to citrate dialysate.

Additional Investigations

HD using an acetate or citrate dialysate was performed 6 times sequentially. The composition of the 2 dialysates is listed in Table 1. The patient gave informed consent to undergo HD using each dialysate. Both treatments were performed under the same conditions using an APS-13S polysulfone membrane (Asahi Medical, Tokyo, Japan) with the same dry weight and ultrafiltration rate. Dialysate flow and blood flow were 500 and 150 mL/min, respectively. Each treatment lasted 180 minutes, with use of 500 U/h of heparin. BP and heart rate were measured every 30 minutes. A Crit-Line III TOA (JMS Corp, Tokyo, Japan) was used to monitor the change in blood volume, and a Physio Flow Lab-1 impedance cardiograph (Manatec Biomedical, Macheren, France) was used to evaluate hemodynamic status by noninvasive measurement of cardiac output and systemic vascular resistance.¹⁶ Blood samples were collected before (from systemic arterial circulation), at the midpoint, and after (from the arterial dialysis tubing) HD to determine pH and bicarbonate, ionized calcium, acetoacetic acid, 3-hy-

Table 1. Composition of Acetate and Citrate Dialysates

	Acetate	Citrate
Sodium (mEq/L)	140	140
Chloride (mEq/L)	111	111
Calcium ion (mEq/L)	3	3
Magnesium (mEq/L)	1.0	1.0
Potassium (mEq/L)	2.0	2.0
Glucose (mg/dL)	100	150
Bicarbonate (mEq/L)	25	35
Acetate (mg/dL)	60	0
Citrate (mg/dL)	0	12.8
Final pH	7.0-7.8	7.5-8.0
Osmolality (mOsm/kg)	296	298

Note: Conversion factors for units: calcium ion and magnesium in mEq/L to mmol/L, $\times 0.5$; glucose in mg/dL to mmol/L, $\times 0.05551$; citrate in mg/dL to μ mol/L, $\times 52.05$. No conversion is necessary for sodium, chloride, potassium, and bicarbonate levels expressed in mmol/L and mEq/L and osmolality expressed in mmol/kg and mOsm/kg.

droxybutyric acid, and acetate levels. Acetoacetic acid and 3-hydroxybutyric acid were assayed enzymatically by using 3-HB (for 3-hydroxybutyric acid) and Total Ketone Body kits (Kainos Laboratories, Tokyo, Japan), and acetate was assayed by using an F-kit (R-Biopharm AG, Darmstadt, Germany).

Data are presented as mean $\pm$ SD. Statistical significance was evaluated by using a paired *t* test with *P* < 0.05 considered to indicate a significant difference. Estimated glomerular filtration rate was calculated by using the formula $194 \times \text{Creatinine}^{-1.094} \times \text{Age}^{-0.287} \times 0.739$.¹⁷

Diagnosis

Comparison of clinical data during HD with the 2 dialysates (Table 2) showed that minimal systolic BP, minimal diastolic BP, and post-HD diastolic BP were significantly lower when the acetate dialysate was used. Minimal heart rate was also lower in HD with the acetate dialysate, and the decrease in BP during acetate dialysis often led to discontinuation of dialysis before the dry weight could be reached. Consequently, the decrease in circulating blood volume and final weight loss were significantly lower with the acetate dialysate.

Representative hemodynamic parameters monitored by using Physio Flow Lab-1 are shown in Fig 1 for both dialysates. With the acetate dialysate, BP decreased suddenly at 2 hours into the dialysis session with no increase in heart rate or systemic vascular resistance; that is, vascular tone failed to increase and BP decreased. In contrast, BP and systemic vascular resistance remained constant during HD with the citrate dialysate.

Biochemical parameters before, during, and after HD with the 2 dialysates are listed in Table 3. Pre-HD acetate levels did not differ significantly between the 2 dialysates. However, as expected, the mid- and post-HD levels of acetate were greater with the acetate dialysate. The pH and bicarbonate levels at the midpoint of HD with the

Table 2. Clinical Data for HD With Acetate or Citrate Dialysate

	Acetate	Citrate	P
Set dry weight (kg)	32.2 ± 0.2	32.2 ± 0.2	0.5
Set ultrafiltration rate (L/h)	0.71 ± 0.08	0.75 ± 0.03	0.3
Systolic blood pressure (mm Hg)			
Pre-HD	153.7 ± 4.9	158.7 ± 11.6	0.4
Minimum during HD	85.3 ± 2.7	117.7 ± 6.7	<0.001
Post-HD	129.7 ± 18.5	137.7 ± 2.2	0.3
Diastolic blood pressure (mm Hg)			
Pre-HD	110.0 ± 6.2	110.0 ± 3.2	0.9
Minimum during HD	42.7 ± 5.9	76.0 ± 3.5	<0.001
Post-HD	84.0 ± 14.7	109.3 ± 9.2	0.03
No. of interventions for hypotension	8	0	
Heart rate (beats/min)			
Pre-HD	75.7 ± 3.6	76.0 ± 3.5	0.9
Minimum during HD	50.7 ± 2.1	66.0 ± 9.5	0.003
Post-HD	66.0 ± 4.7	69.0 ± 3.2	0.2
Pre-HD weight (kg)	34.3 ± 0.2	34.4 ± 0.2	0.7
Post-HD weight (kg)	32.4 ± 0.2	32.0 ± 0.1	0.04
Final weight loss (kg)	1.9 ± 0.1	2.4 ± 0.2	0.02
Change in blood volume (%)*	-19.5 ± 0.5	-21.6 ± 1.3	0.02

Abbreviation: HD, hemodialysis.

*Measured on a Crit-Line instrument.

citrate dialysate were significantly greater than with the acetate dialysate. However, there were no significant differences in pH and bicarbonate levels after HD with the 2 dialysates and no significant difference in ionized calcium levels at any time. Acetoacetic acid and 3-hydroxybutyric acid levels with the citrate dialysate were lower than those with the acetate dialysate. We then compared levels of ketone bodies at the post-HD

time with pre-HD amounts and expressed these as ratios. With acetate dialysate, the relative levels of post-HD acetoacetic acid (2.06) and 3-hydroxybutyric acid (2.79) were significantly different from the initial levels ($P = 0.001$ and $P < 0.001$, respectively), whereas with citrate dialysate, the relative post-HD levels of acetoacetic acid (1.23) and 3-hydroxybutyric acid (1.35) were not significantly different from the initial levels ($P = 0.2$ and $P = 0.1$, respectively).

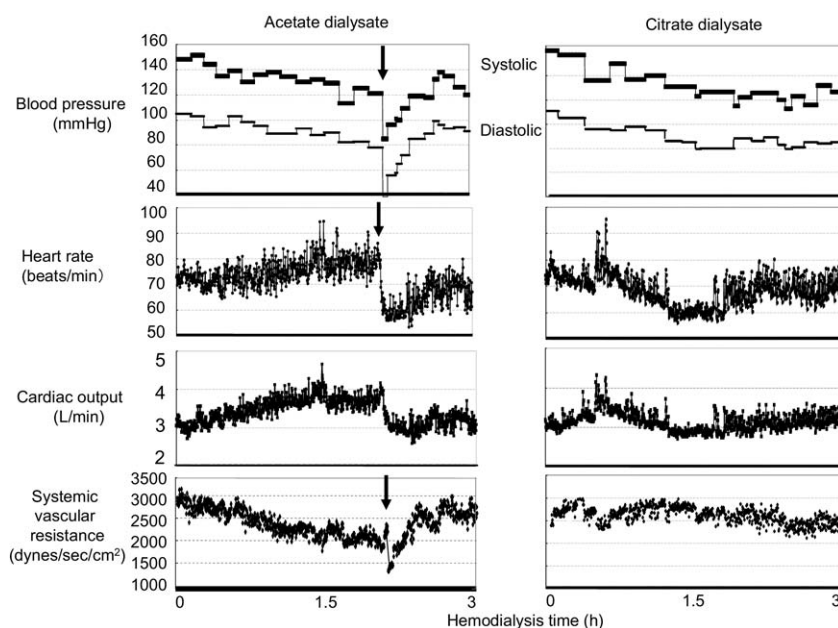


Figure 1. Changes in hemodynamic parameters during hemodialysis (HD) with acetate-containing bicarbonate dialysate or acetate-free citrate dialysate. With acetate dialysate, blood pressure (BP) decreased suddenly at 2 hours into the dialysis session (arrow), and heart rate failed to increase to compensate for hypotension. The volume of cardiac output did not change and systemic vascular resistance was not increased at this time. With citrate dialysate, BP was maintained and systemic vascular resistance was stable throughout the HD session. Parameters were measured using Physio Flow Lab-1.

Table 3. Comparison of Pre-, Mid-, and Postdialysis Biochemical Parameters

	Acetate Dialysate	Citrate Dialysate	P
Acetate (mg/dL)			
Pre-HD	1.14 ± 0.23	1.19 ± 0.28	0.3
Mid-HD	18.33 ± 9.38	0.98 ± 0.47	0.008
Post-HD	15.05 ± 8.93	0.72 ± 0.18	0.01
pH			
Pre-HD	7.34 ± 0.04	7.36 ± 0.02	0.4
Mid-HD	7.41 ± 0.02	7.45 ± 0.02	0.02
Post-HD	7.46 ± 0.02	7.45 ± 0.02	0.8
Bicarbonate (mEq/L)			
Pre-HD	13.9 ± 2.8	16.6 ± 0.9	0.07
Mid-HD	18.2 ± 1.8	22.8 ± 2.0	0.01
Post-HD	19.6 ± 2.1	22.7 ± 2.2	0.07
Calcium ion (mEq/L)			
Pre-HD	2.31 ± 0.21	2.26 ± 0.23	0.8
Mid-HD	2.47 ± 0.23	2.26 ± 0.28	0.3
Post-HD	2.50 ± 0.16	2.34 ± 0.16	0.2
Acetoacetic acid (mg/dL)			
Pre-HD	3.05 ± 2.67	0.74 ± 0.18	0.06
Mid-HD	3.29 ± 2.66	0.49 ± 0.07	0.03
Post-HD	5.54 ± 3.35	0.98 ± 0.54	0.01
3-Hydroxybutyric acid (mg/dL)			
Pre-HD	4.52 ± 4.16	1.21 ± 0.35	0.08
Mid-HD	4.01 ± 3.74	0.61 ± 0.29	0.05
Post-HD	9.75 ± 3.98	1.84 ± 1.07	0.001
Ratio of acetoacetic acid levels			
Mid-HD v pre-HD	1.11	0.67	<0.001
Post-HD v pre-HD	2.06	1.23	0.01
Ratio of 3-hydroxybutyric acid levels			
Mid-HD v pre-HD	0.90	0.48	<0.001
Post-HD v pre-HD	2.79	1.35	0.02

Note: Values expressed as mean ± SD based on 6 dialysis sessions per buffer. For ratios of acetoacetic acid and 3-hydroxybutyric acid, raw values were log transformed before calculating the mean and performing *t* tests. Normal ranges of serum acetoacetic acid and 3-hydroxybutyric acid in HD patients are 0.14 to 0.69 and 0 to 0.77 mg/dL, respectively, similar to those in patients with normal kidney function. Conversion factors for units: calcium ion in mEq/L to mmol/L, ×0.5; acetoacetic acid in mg/dL to mmol/L, ×0.09795; 3-hydroxybutyric acid in mg/dL to μmol/L, ×96.05; acetate in mg/dL to mmol/L, ×0.167. Bicarbonate levels expressed in mEq/L and mmol/L are equivalent.

Abbreviation: HD, hemodialysis.

Clinical Follow-up

The patient was discharged from our hospital after 1 month and has continued HD therapy with citrate dialysate as an outpatient. She and her family have expressed a desire for future kidney transplantation.

DISCUSSION

The patient in this case experienced frequent hypotension during HD with an acetate-containing dialysate, but her BP stabilized after a switch to a citrate dialysate. The citrate dialysate may have improved the circulatory dynamics during HD because of differences in glucose and bicarbonate levels, a direct effect of citrate, and the absence of acetate in the dialysate. Acetate can

induce nitric oxide, a vasodilator^{18,19} that can cause intradialytic cardiovascular instability,^{20,21} and the mid- and post-HD acetate levels were 10 to 15 times greater than the pre-HD level in our patient during HD with acetate dialysate. These levels are greater than reported previously²² and indicate that the acetate load led to hemodynamic instability.

Ketone bodies (acetoacetic acid and 3-hydroxybutyric acid) are produced from acetyl-CoA by means of β-oxidation of fatty acids, and hyperketonemia arises from overproduction of ketone bodies in the liver because of reduced insulin action. In patients with MMA, fatty acid metabolism is disturbed because of methylmalonyl-CoA

mutase deficiency, and this leads to accumulation of ketone bodies. Methylcitric acid and branched-chain amino acids accumulate in serum and also are converted to ketone bodies, making ketoacidosis a common symptom of MMA. Hyperglycemia also occurs commonly in patients with MMA, which suggests a disruption of insulin action.

Acetate normally is metabolized in the liver and converted to acetyl-CoA. Acetyl-CoA is the substrate for production of ketone bodies and also is metabolized through the citric acid cycle. In our patient, post-HD ketone body and acetate levels were significantly greater with acetate dialysate than citrate dialysate. These results suggest that all metabolic pathways including ketogenesis were activated to metabolize acetate when acetate dialysate was used in patients with MMA.

Citrate dialysate has several advantages. Rapid correction of acidosis is possible because of the greater bicarbonate concentration. Citrate dialysate contains 12.8 mg/dL (667 $\mu\text{mol/L}$) of citrate instead of acetate for adjusting pH. Citrate has a long history of use in medicine as an anticoagulant and has the ability to chelate calcium ions. Citrate is metabolized in liver and muscle. The citric acid cycle is fully functional in patients with MMA, and citrate is metabolized by direct entry into this cycle. The ketogenesis pathway is not activated by citrate dialysate because citrate is not converted to acetyl-CoA. These advantages suggest that acetate-free citrate dialysate is suitable for patients with MMA to avoid the development of ketoacidosis.

The case presented here highlights the metabolic and hemodynamic advantages of citrate dialysate and shows the importance of avoiding acetate accumulation in patients using HD for end-stage renal disease caused by MMA.

ACKNOWLEDGEMENTS

Support: None.

Financial Disclosure: None.

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