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Acid-base changes and acetate metabolism during routine and high-efficiency hemodialysis in children

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Acid-base changes and acetate metabolism during routine and high-efficiency hemodialysis in children. Changes in acid-base status and plasma acetate concentrations were studied in eight children during 11 hemodialysis sessions. During dialysis, the blood bicarbonate concentration fell (20.5 ± 0.7 to 19.6 ± 0.8 mEq/liter), the P_{CO_2} fell (33.4 ± 0.8 to 27.5 ± 1.4 mm Hg), and the pH rose (7.42 ± 0.01 to 7.48 ± 0.02). During the hour after dialysis, the bicarbonate concentration rose to normal (23.4 ± 0.7 mEq/liter), the P_{CO_2} rose (32.8 ± 0.8 mm Hg), and the pH remained unchanged. The half-life of plasma acetate, measured after dialysis, was 8.7 min. During five "high-efficiency" dialysis sessions (urea clearance, > 3.0 ml/min/kg), blood bicarbonate concentration fell 3.2 mEq/liter, P_{CO_2} fell 8.7 mm Hg, and plasma acetate rose to 7.51 mmoles/liter, whereas during six "routine efficiency" dialysis sessions (urea clearance, 1.5 to 3.0 ml/min/kg), blood bicarbonate rose 1.0 mEq/liter, P_{CO_2} fell 36 mm Hg, and plasma acetate rose to 3.52 mmoles/liter. At 1 hour after the end of dialysis, blood bicarbonate, P_{CO_2}, and plasma acetate concentrations were similar in the two groups. Clinical problems occurred more frequently in the high-efficiency group during dialysis although the difference was not significant. The data indicate that *(1)* dialysis with acetate buffer effectively corrects predialysis metabolic acidosis, *(2)* although children have a high rate of acetate metabolism, during high-efficiency dialysis this rate is exceeded by the influx of acetate, and acid-base abnormalities occur. These abnormalities are transient but may cause clinical problems.

Modifications acido-basiques et métabolisme de l'acétate au cours de l'hémodialyse de routine ou à efficacité élevée chez l'enfant. Les modifications de l'état acido-basique et des concentrations plasmatiques d'acétate ont été étudiées chez huit enfants au cours de 11 séances d'hémodialyse. Au cours de la dialyse les bicarbonates diminuent (20,5 ± 0,7 à 19,6 ± 0,8 mEq/litre), la P_{CO_2} diminue (33,4 ± 0,8 à 27,5 ± 1,4 mm Hg), et le pH augmente (7,42 ± 0,01 à 7,48 ± 0,02). Au cours de l'heure qui suit la dialyse les bicarbonates s'élèvent à une valeur normale, 23,4 ± 0,07 mEq/litre, la P_{CO_2} s'élève à 32,8 ± 0,8 mm Hg, et le pH est inchangé. La demi vie de l'acétate plasmatique, mesurée après la dialyse, était de 8,7 min. Au cours de cinq séances de dialyse à haute efficacité (clearance de l'urée, > 3,0 ml/min/kg) les bicarbonates baissent de 3,2 mEq/litre, la P_{CO_2} de 8,7 mm Hg, et l'acétate plasmatique s'est élevé à 7,51 mmoles/litre alors qu'au cours de six séances de dialyse d'efficacité moyenne (clearance de l'urée, 1,5 à 3,0 ml/min/kg) les bicarbonates ont augmenté de 1,0 mEq/litre, la P_{CO_2} a diminué de 3,6 mm Hg, et l'acétate plasmatique s'est élevé à 3,52 mmoles/litre. Une heure après la fin de la dialyse les bicarbonates, la P_{CO_2} et l'acétate plasmatique étaient semblables dans les deux groupes. Des problèmes cliniques sont survenus plus souvent au cours de la dialyse dans le groups à haute efficacité bien que la différence ne soit pas significative. Ces résultats indiquent que *(1)* la dialyse avec le tampon acétate corrige efficacement l'acidose métabolique prédialytique, *(2)* bien que l'enfant ait une capacité élevée de métaboliser l'acétate, cette capacité est débordée, au cours de la dialyse à haute efficacité, par l'entrée d'acétate et des anomalies acidobasiques surviennent. Ces anomalies sont transitoires et peuvent déterminer des problèmes cliniques.

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End-stage renal disease leads to many metabolic disorders, one being chronic metabolic acidosis. Hemodialysis treatment corrects this acidosis by supplying the patient with a buffer source. The most frequently used buffer is sodium acetate. During hemodialysis, the patient receives acetate that must be metabolized in order to generate bicarbonate. At the same time, however, bicarbonate is removed by the dialysis process. If the rate of acetate infusion is greater than the patient's ability to metabolize it, acetate will be accumulated by the patient. Similarly, if the rate of bicarbonate removal exceeds the rate at which bicarbonate is generated from acetate, metabolic acidosis will worsen during dialysis. Therefore, the effectiveness of the acid-base correction by hemodialysis depends on the balance between the efficiency of dialysis (rate of transfer of acetate and bicarbonate) and the patient's ability to metabolize acetate.

Acid-base homeostasis and acetate metabolism during dialysis have been studied in adults, but

there is little information available on children. Two earlier studies [1, 2] suggested that some hemodialysis patients metabolized acetate slowly; they were defined as "acetate intolerant." These patients were identified by the development of high concentrations of plasma acetate and worsening acidosis during dialysis. A later study [3] established that high-efficiency dialysis (the use of large surface area artificial kidneys and high blood flow rates) in adults caused worsening acidosis and other adverse metabolic effects during dialysis. A recent study [4] reported that the use of bicarbonate instead of acetate in the dialysate resulted in better patient tolerance of hemodialysis. At present, the relative importance of the efficiency of dialysis and of the patient's metabolic capacity in determining acetate and acid-base metabolism is unclear. In addition, the metabolic capacity of children for acetate has not been defined.

Our study was designed to define the acid-base and acetate changes during acetate-based hemodialysis and the effectiveness of hemodialysis in correcting metabolic acidosis in children. In addition, the effect of high-efficiency hemodialysis on acid-base homeostasis during dialysis was evaluated.

Methods

Patients. Acid-base homeostasis and acetate metabolism were investigated during 11 hemodialysis sessions for five girls and three boys, 6 to 17 years of age, at The Children's Renal Center of the University of California at San Francisco after informed consent was obtained. Individual patient data are listed in Table 1. Three children (patients 1, 7, and 8) were studied twice, once during their first week of hemodialysis and again after at least 6 weeks of intermittent hemodialysis. All other patients had been undergoing chronic hemodialysis for at least 6 months, except for patient 5 who was studied only during her first week of dialysis. None of the children had diabetes mellitus, hepatic insufficiency, or heart failure.

Hemodialysis procedures. Using Drake-Willock volume-proportioning dialysis units (#4015) and Cobe dialysate without glucose, we prepared and primed the artificial kidneys (Cordis Dow 1.3 Hollow Fiber, Gambro Optima 13.5 and 17, and Gambro Minor) in the usual manner. The size and type of artificial kidney, the rate of blood flow, the rate of ultrafiltration, and the heparinization procedures were chosen by the staff of the dialysis unit based on the needs of each patient. Therefore, only the method of beginning and ending dialysis and the collection of blood and dialysate samples were modified to fit the experimental procedure.

In children with arteriovenous shunts, the shunts were opened, heparin was injected, and the arterial and venous sides of the shunt were clamped. In children with arteriovenous fistulas, the arterial needle was placed against the direction of blood flow, and the venous needle was placed in the direction of blood flow, the two needles separated as much as possible to minimize the degree of arterial-venous mixing. Before connecting the child to the blood lines of the dialysis system, we pumped 800 ml of 0.9% saline through the blood side of the system to remove any acetate that had diffused from the dialysate to the blood side of the system. Then we connected the child to the blood lines but left arterial and venous lines clamped. After setting the blood pump to the correct flow rate, we abruptly began hemodialysis by unclamping the arterial blood line, turning on the dialysis machine and blood pump, and unclamping the venous line in rapid succession ($t = 0$, where t is time). During the 4 hours of dialysis, we collected all outflowing dialysate in a sealed vat for measurement of dialysate volume. After 4 hours of hemodialysis, we abruptly ended dialysis by clamping the venous line, turning off the machine and blood pump, and clamping the arterial line ($t = 240$ min). The abrupt beginning and ending of the hemodialysis session allowed for more accurate measurement of both the gain and loss of substances during dialysis and the changes of plasma acetate during and after hemodialysis. After the end of hemodialysis, the blood remaining in the blood lines and artificial kidney was recirculated for 1 hour, while the disappearance curve of acetate from the body was measured. Finally, we reinfused the recirculating blood.

Collection and analysis of samples: (1) Collection. Blood for measurement of plasma acetate concentration was collected immediately before hemodialysis ($t = 0$), at 5, 10, 15, 30, 60, 120, 180, and 240 min after hemodialysis began and at 2, 5, 10, 15, 30, and 60 min after hemodialysis ended. Blood for measurement of pH, P_{CO_2}, and bicarbonate was collected before dialysis, at 30, 60, 120, 180, and 240 min after dialysis began, and at 60 min after dialysis ended. Blood for measurement of the concentrations of plasma organic acids was collected prior to dialysis, at the end of dialysis (240 min), and 60 min after dialysis. Dialysate samples, both inflowing (D_i) and outflowing (D_o) were collected for determination of acetate, P_{CO_2}, and total carbon dioxide

content and bicarbonate at 30, 60, 120, 180, and 240 min after the start of dialysis.

(2) Plasma and dialysate acetate. Blood samples were collected from the arterial blood line in heparinized syringes and were immediately injected into heparinized tubes and centrifuged to separate the plasma from the red blood cells. The plasma was placed in stoppered test tubes and kept on ice until the experiment was completed and was then frozen at −20° C until the time of analysis. After deproteinization and vacuum microdistillation of the plasma, plasma acetate was measured by gas chromatography as previously described [5]. Dialysate samples were not deproteinized or vacuum distilled but were diluted with water (1:40) and measured directly by gas chromatography.

(3) Blood pH, PCO_2, and bicarbonate and dialysate PCO_2. Blood and dialysate samples were collected in heparinized syringes, kept in ice, and analyzed within 30 min. Blood pH, PCO_2, bicarbonate, and dialysate PCO_2 were measured on a blood-gas analyzer (Corning).

(4) Dialysate total carbon dioxide content and bicarbonate. Dialysate samples were collected in syringes, injected into rubber stoppered tubes, and kept frozen until analysis. Total carbon dioxide was determined with a total carbon analyzer (Oceanography International, College Station, Texas) as follows. The sample was injected into a chamber of the analyzer that contains 5 N phosphoric acid and converts all bicarbonate to carbon dioxide. The solution was continually flushed with carbon-dioxide-free nitrogen, and all carbon dioxide was carried past the infrared detector, which measures a peak of carbon dioxide absorption. The area under the peak was measured by an integrator with a digital readout. The measurement of the sample was compared with measurements of standard sodium carbonate solutions to calculate total carbon dioxide. Dialysate bicarbonate was calculated from the measured PCO_2 (Corning blood gas analyzer) and total carbon dioxide as follows:

$$[HCO_3^-] = [\text{total } CO_2] - [0.03 \times PCO_2]$$

(5) Organic acids. Lactate, pyruvate, citrate, β-hydroxybutyrate, and acetoacetate were measured in the frozen plasma samples collected in the same manner as the acetate plasma samples. The plasma was deproteinized with perchloric acid, and the concentrations of the organic acids were determined with NAD-linked enzymatic assays according to procedures described by Bergmeyer [6].

Abbreviations and formulas. The following abbreviations are used:

Q = flow rate (*ml/min*)
c = concentration (mEq/*liter* or mM)
D_i = incoming dialysate
D_o = outgoing dialysate
B_i = incoming (arterial) blood
Q_f = ultrafiltration flow rate (*ml/min*)
U_k = ultrafiltration constant
TMP = transmembrane pressure (*mm Hg*)
N = flux rate, (i.e. transfer rate of a solute to or from the dialysate)
D = dialysance (*ml/min*)
C = clearance (*ml/min*)
Bic = bicarbonate
Ac = acetate
Oa = organic acids
$t^1/_2$ = half life (*min*)

The following formulas [7] are used:

$$N = Q_{Do} \times c_{Do} - Q_{Di} \times c_{Di}$$

$$D = \frac{N}{c_{Bi} - c_{Di}}$$

$$C = \frac{N}{c_{Bi}}$$

Calculation of acid-base mass balance during hemodialysis. Total base equivalents received during dialysis equals the acetate infused minus the loss of bicarbonate and organic acids; that is, total base = Ac gain − Bic loss − Oa loss.

Acetate infused during dialysis was determined by measuring the rate of transfer or flux (N) of acetate at 0.5, 1, 2, 3, and 4 hours during dialysis, and multiplying by the number of minutes in the period that the measurement represented (for example, N at 1 hour × 30 min = acetate infused between 0.5 and 1 hour). The total acetate gain for one dialysis session was the sum of the acetate infused during all the periods. The rate of transfer of acetate was determined from the rate of loss from the dialysate as follows:

$$N_{Ac} = Q_{Di} \times c_{Di(Ac)} - Q_{Do} \times c_{Do(Ac)}$$

Q_{Do} was determined by dividing the weight of the dialysate collected over a timed period by the number of minutes in that period. c_{DiAc} and $c_{Do(Ac)}$ were measured as described in the analysis of the plasma samples. Q_{Di} was calculated as follows:

$$Q_{Di} = Q_{Do} - Q_f$$

$$Q_f = U_k \times TMP$$

TMP was calculated from the pressure gauges of the dialysis machine. U_k is different for each artificial kidney. The U_k values (*ml/hr/mm Hg*) are 1.8 for the C-DAK-1.3, 1.32 for the Gambro minor, 2.5 for the Gambro Optima-17, and 4.4 for the Gambro Optima-13.5. Therefore,

$$N_{Ac} = (Q_{Do} - Q_f) \times c_{Di(Ac)} - Q_{Do} \times c_{Do(Ac)}$$

The total bicarbonate lost during dialysis was determined by measuring the rate of transfer of bicarbonate in the same manner as described for acetate. The transfer of bicarbonate is determined from the gain of bicarbonate by the dialysate according to the following formula:

$$N_{\widehat{Bio}} = Q_{\widehat{Do}} \times c_{Do(Bic)} - (Q_{Do} - Q_f) \times c_{Di(Bic)}$$

The total organic acid lost during dialysis was estimated from the end-dialysis plasma concentration of each organic acid and the previous published values for the dialysance of each organic acid (for example, total lactate lost = $c_{lactate}$ (*mmoles/ml*) × $D_{lactate}$ (*ml/min*) × 240 min). The amount lost for each organic acid was summed to give an estimate of total organic acid lost. All organic acid concentrations represent equimolar concentrations of potential bicarbonate except citrate, which is a tricarboxylic acid and can yield 3 moles of bicarbonate per mole of citrate.

Estimate of the patient's rate of acetate metabolism by plasma half-life ($t^1/_2$). Using the MLAB computer program developed at the National Institute of Health, we fitted the decreasing concentrations of plasma acetate after hemodialysis ended to a monoexponential disappearance curve and calculated the half-life, which was taken as an estimate of the patient's rate of acetate metabolism.

Correlations. The changes resulting from hemodialysis (blood bicarbonate concentration, plasma acetate concentration, and base transfer) were correlated with the two factors controlling the acid-base changes during dialysis: efficiency of dialysis and the patient's rate of acetate metabolism ($t^1/_2$). To estimate the efficiency of dialysis, we divided the clearance of urea and the dialysance of acetate by the weight of the patient. The urea clearance was calculated from published data [8–10] for the artificial kidney used and the patient's blood flow. The dialysance of acetate was measured by the formula previously given.

High efficiency hemodialysis. In children, effective hemodialysis is defined by a urea clearance (C_{urea}) of 2 to 3 ml/min/kg of body wt [11]. Dialysis sessions were divided into a high-efficiency group, $C_{urea} > 3$ ml/min/kg, and a routine-efficiency group, $C_{urea} \leq 3$ ml/min/kg. There were five studies in the high-efficiency group and six in the routine group. Two patients (1 and 8) were studied in both groups. The two groups were compared for changes in acid-base status, plasma acetate, balance of base transfer, and clinical problems. The clinical problems evaluated were the episodes of hypotension requiring saline infusion and the episodes of nausea and vomiting recorded by the staff during dialysis.

Statistical analysis. The high- and routine-efficiency groups were compared by Student's *t* test and the Mann-Whitney test, when indicated. Correlations were performed by linear regression analysis by the method of least squares.

Results

Effects of hemodialysis on blood pH, P_{CO_2}, and bicarbonate and on plasma acetate (Table 1, Fig. 1). During hemodialysis, the blood pH rose from a predialysis value of 7.42 ± 0.01 to an end-dialysis value of 7.48 ± 0.02 ($P < 0.002$). This rise of pH was due to a decrease in P_{CO_2} from 33.4 ± 0.8 to 27.5 ± 1.4 mm Hg ($P < 0.001$) during dialysis. The blood bicarbonate concentration also decreased slightly but not significantly from 20.5 ± 0.7 mEq/liter before dialysis to 19.5 ± 0.8 mEq/liter (P = NS) after the first hour of hemodialysis and then remained unchanged. The plasma acetate concentration increased rapidly during the first hour from a predialysis concentration of 0.06 ± 0.01 to 3.24 ± 0.33 mM ($P < 0.001$) and then slowly rose to 5.32 ± 0.82 ($P < 0.001$) at the end of dialysis. When hemodialysis ended, the remaining acetate was rapidly metabolized, the concentration falling to 0.13 ± 0.03 mM ($P < 0.001$) at 1 hour after dialysis. During the 1-hour period after dialysis, the bicarbonate concentration rebounded from its end dialysis concentration to 23.4 ± 0.7 mEq/liter ($P < 0.001$) because the remaining acetate was metabolized. During this period, the P_{CO_2} increased from its end-dialysis concentration to 32.8 ± 0.8 mm Hg ($P < 0.001$), and the pH remained unchanged (7.48 ± 0.02) because of the parallel increase of the P_{CO_2} and the bicarbonate.

Effect of hemodialysis on plasma organic acids other than acetate (Table 2). β-Hydroxybutyrate increased significantly during dialysis and remained unchanged at 1 hour after dialysis. Lactate de-

Table 1. Pediatric hemodialysis descriptive patient and dialysis information, acetate and bicarbonate changes during hemodialysis, and balance of base equivalents resulting from hemodialysis

Patients	Age *Yr*	Weight *kg*	Acetate $t^1/_2$ *min*	Type of kidney[a]	C_{Urea} *ml/kg/min*	D_{Ac} *ml/kg/min*	Q_F[b] *ml/kg/hr*	Blood bicarbonate, *mEq/liter* Before dialysis	End of dialysis	1 Hr after dialysis
1a	10 7/12	32.2	11.0	G. Minor	2.17	1.63	1.4	18.4	21.1	22.8
1b	11 1/12	33.5	11.9	C-DAK 1.3	3.28	2.60	4.0	22.6	16.7	22.4
2	10 10/12	27.2	6.6	G. Minor	2.76	2.43	1.5	17.7	19.0	19.4
3	15 6/12	60.0	5.3	G. 13.5	2.37	1.52	8.4	22.3	21.5	24.0
4	17 5/12	73.8	9.4	G. 17.0	1.49	1.20	2.5	20.9	18.8	20.6
5	11 11/12	25.4	9.2	G. Minor	2.95	2.29	13.5	16.1	17.7	23.2
6	13 2/12	40.9	12.8	C-DAK 1.3	3.50	2.65	5.2	20.8	18.9	23.4
7a	13 1/12	35.9	10.7	C-DAK 1.3	3.48	2.88	2.0	20.6	15.8	23.8
7b	13 3/12	37.7	9.2	C-DAK 1.3	3.05	2.21	3.9	22.8	19.4	27.5
8a	6 6/12	19.4	5.10	G. Minor	3.10	3.39	8.9	21.7	21.9	24.9
8b	6 9/12	20.2	4.0	G. Minor	2.97	2.45	10.1	21.1	24.3	25.8
Mean	11 9/12	36.9	8.7		2.83	2.30	5.6	20.5	19.6	23.4
± SEM		±5.0	±0.9		±0.18	±0.64	±1.2	±0.7	±0.8	±0.7

[a] Artificial kidney, type and size (surface area): C-DAK 1.3, Cordis Dow Hollow Fiber (1.3 m²); G. Minor, Gambro Lundia Minor, Parallel Plate (0.54 m²); G-13.5, Gambro Lundia Optima 13.5, Parallel Plate (1.0 m²); G-17.0, Gambro Lundia Optima 17.0, Parallel Plate (1.02)

[b] D_{Ac} is acetate dialysance; Q_F is ultrafiltration flow rate.

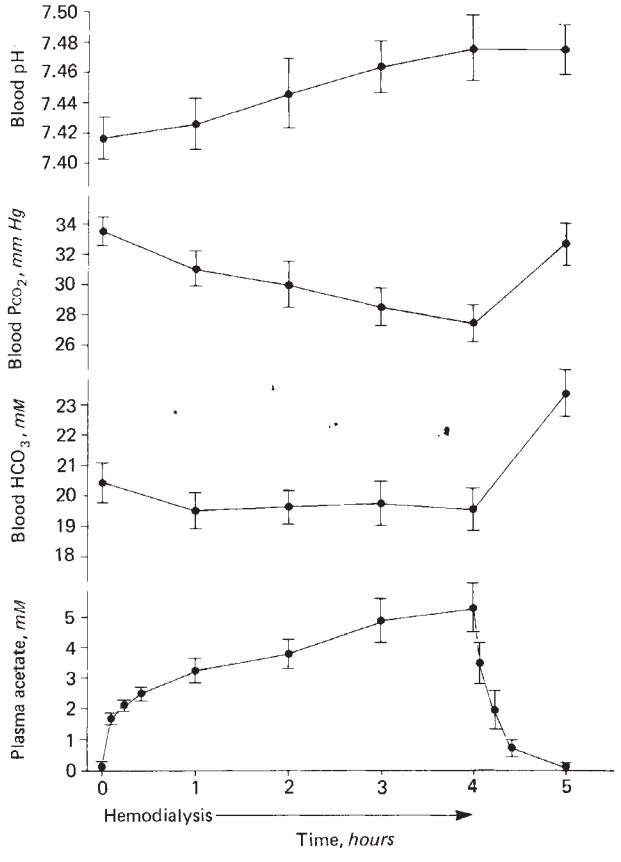

Fig. 1. *Acid-base and acetate changes during 11 hemodialysis procedures in children.* Data are the means ± SEM.

creased significantly during dialysis but returned toward its predialysis concentration at 1 hour after dialysis. Citrate did not change significantly from predialysis to 1 hour after dialysis. The concentrations of pyruvate and acetoacetate both fell significantly during dialysis, but their concentrations were so low, they had little effect on the overall organic acid change. The sum of the concentrations of all five organic acids increased from 2.1 mM before dialysis to 2.8 mM at the end of dialysis and to 3.1 mM at 1 hour after dialysis.

Balance of base equivalents during hemodialysis (Table 1). During hemodialysis, the children received 19.2 ± 1.4 mmoles/kg body wt acetate and lost 12.7 ± 0.1 mmoles/kg of body wt bicarbonate. In addition to the loss of bicarbonate, the children also lost organic acids, which, like acetate, are potential base equivalents. The combined losses of the organic acids were estimated to be 1.7 ± 0.2 mmoles/kg/dialysis. Therefore, the amount of potential base gain per dialysis was 4.9 ± 0.9 mmoles/kg. Because the patients were dialyzed three times per week, they received 14.7 mmoles/kg/week of potential base, or 2.1 mmoles/day.

Plasma acetate half-life. The disappearance of plasma acetate after the end of hemodialysis was fitted to a monoexponential decay curve. As determined by this method, the mean $t^1/_2$ of acetate in the plasma was 8.7 ± 0.4 min.

Table 1. *(continued)*

Plasma acetate, mM			Balance of base equivalents, *mmoles*			
Before dialysis	End of dialysis	1 Hr after dialysis	Acetate gain	HCO_3 lost	Organic acid lost	Potential base gain
0.09	1.95	0.06	511	352	28	131
0.03	8.81	0.25	662	482	84	96
0.07	4.97	0.14	556	307	63	186
0.06	2.29	0.05	797	651	48	98
0.04	3.24	0.07	815	475	84	256
0.11	6.41	0.10	513	266	45	202
0.05	7.75	0.32	864	651	54	159
0.09	8.83	0.02	797	480	108	204
0.06	7.92	0.16	651	557	56	38
0.07	4.18	0.07	520	275	27	219
0.02	2.18	0.02	455	332	32	91
0.06 ±0.01	5.32 ±0.82	0.13 ±0.03	649 ±44	349 ±43	57 ±8	153 ±20

Table 2. Effect of hemodialysis on plasma organic acids other than acetate[a]

	Predialysis	End-dialysis[b]	1 Hr after dialysis[b]
Lactate, mM	1.38 ± 0.29	0.86 ± 0.14[c]	1.22 ± 0.26
β-Hydroxybutyrate, mM	0.43 ± 0.09	1.70 ± 0.28[d]	1.61 ± 0.37
Citrate, mM	0.15 ± 0.10	0.16 ± 0.01	0.16 ± 0.01
Pyruvate, mM	0.08 ± 0.01	0.05 ± 0.01[d]	0.06 ± 0.01
Acetoacetate, mM	0.04 ± 0.01	0.01 ± 0.00[d]	0.01 ± 0.00

[a] Data are the means ± SEM of 11 dialysis procedures.
[b] There were no significant differences between end-dialysis and 1-hr postdialysis concentrations.
[c] Significantly different from predialysis concentrations, $P < 0.05$.
[d] Significantly different from predialysis concentrations, $P < 0.01$.

Table 3. Correlation coefficients (r) between the efficiency of dialysis, the metabolic ability to metabolize acetate, and the acid-base changes resulting from hemodialysis[a]

	C_{Urea} (ml/min/kg body wt)	Acetate dialysance (ml/min/kg body wt)	Plasma acetate $t^1/_2$ (min)
Acetate gain during dialysis (mmoles/kg body wt)	0.787[b]	0.965[b]	−0.166
Bicarbonate loss during dialysis (mmoles/kg body wt)	0.843[b]	0.717[c]	−0.024
Potential base gain from dialysis (mmoles/kg body wt)	0.221	0.617[d]	−0.286
End-dialysis plasma acetate concentration (mM)	0.717[c]	0.509	0.632[d]
Change in blood bicarbonate during dialysis (mEq/liter)	−0.317	−0.155	−0.545
Change in blood bicarbonate after dialysis (mEq/liter)	0.594[d]	0.344	0.508

[a] Data are from 11 hemodialysis procedures.
[b] Significant correlation between variables, $P < 0.005$.
[c] Significant correlation between variables, $P < 0.01$.
[d] Significant correlation between variables, $P < 0.05$.

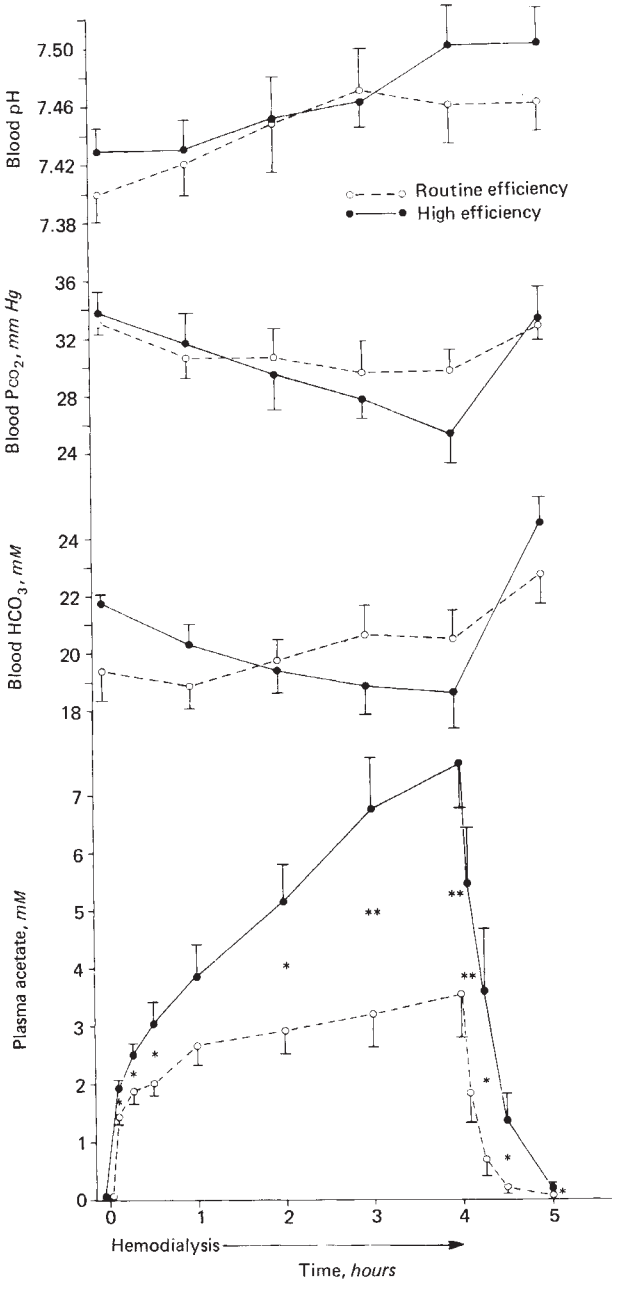

Fig. 2. *Acid-base and acetate changes in children undergoing either routine efficiency (N = 6) or high efficiency (N = 5) hemodialysis.* Data are the means ± SEM. Symbols denoting statistical significance between the concentrations of the routine and high efficiency groups are $*P < 0.001$, $**P < 0.05$.

Correlations (Table 3). By correlating both the efficiency of dialysis (measured by urea clearance and dialysance of acetate factored for body weight) and the child's ability to metabolize acetate (measured by plasma half-life) to the change in plasma acetate, the change in blood bicarbonate, and the potential base gain, we attempted to evaluate the relative importance of dialysis efficiency and metabolic capacity for determining acid-base homeostasis resulting from dialysis. Both measures of dialysis efficiency had a significant positive correlation with acetate gain and bicarbonate loss, but only D_{Ac} had a significant correlation to potential base gain. Plasma half-life showed no correlation with acetate gain, base loss, or potential base gain. Both urea clearance and plasma half-life had a significant correlation to end-dialysis acetate concentration. Neither the measures of dialysis efficiency nor the plasma half-life correlated with the change in bicarbonate during dialysis.

Effect of high-efficiency hemodialysis (Fig. 2, Table 4). The ages, weights, predialysis acid-base status, and plasma half-life of acetate were similar in the children treated with high-efficiency dialysis ($C_{urea} > 3$ ml/min/kg) and routine-efficiency dialysis ($C_{urea} \leq 3$ ml/min/kg). In addition, there was no significant difference in the rate of ultrafiltration between the groups. Because of the manner in which the groups were defined, the clearance of urea per kilogram and the dialysance of acetate per kilogram were significantly greater in the high-efficiency group.

The changes in blood gases during dialysis were markedly different between the two groups (Fig. 2, Table 4). The bicarbonate concentration fell by 3.2 ± 1.1 mEq/liter in the high-efficiency group and rose by 1.0 ± 0.8 mEq/liter in the routine-efficiency group ($P < 0.05$). Although the Pco_2 fell by 8.7 ± 2.0 mm Hg in the high-efficiency group, it fell only by 3.6 ± 0.8 mm Hg in the routine-efficiency group ($P < 0.05$). The result of these changes was an almost identical rise in pH in the two groups.

In the hour after dialysis, the increase in both bicarbonate concentration and Pco_2 was significantly greater in the high-efficiency group, 5.9 ± 1.0 mEq/liter and 8.0 ± 1.4 mm Hg, respectively, than in the routine-efficiency group, 2.2 ± 0.7 mEq and 3.1 ± 1.1 mm Hg, respectively ($P < 0.05$ for both). The pH remained unchanged in both groups.

The plasma acetate concentrations were significantly greater in the high-efficiency group throughout the entire procedure (Fig. 2). The plasma acetate of the high-efficiency group rose rapidly in the first hour of dialysis and continued to rise through the entire dialysis session. In the routine-efficiency group, plasma acetate rose rapidly in the first hour of dialysis but then reached a steady state. At the

end of dialysis, the high-efficiency group had an acetate concentration twice that of the routine-efficiency group (7.51 ± 0.86 vs. 3.52 ± 0.55 mM, $P < 0.001$). Plasma acetate fell rapidly after completion of dialysis in both groups, but the high-efficiency group maintained significantly higher acetate concentrations up to and including 1 hour after dialysis.

The balance of base equivalents was similar in the two groups. Patients in the high-efficiency group gained more acetate than did patients in the routine-efficiency group (21.5 ± 1.6 vs. 17.2 ± 1.8 mmoles/kg, P = NS), but the high-efficiency group lost more bicarbonate (14.5 ± 0.5 vs. 11.1 ± 1.3 mmoles/kg, $P < 0.05$). Therefore, both groups received similar amounts of potential base.

Table 4 indicates the incidence of several clinical problems during hemodialysis treatments. Although the occurrence of hypotension, nausea, and vomiting was more frequent during high-efficiency dialysis than it was during routine-efficiency dialysis, the difference was not statistically significant.

Discussion

The aim of the present study was to evaluate acetate metabolism and acid-base homeostasis of children undergoing conventional hemodialysis. In our study, we evaluated eight children during 11 different dialysis sessions, with dialysate containing 38 mM acetate. During dialysis, blood bicarbonate decreased slightly (20.0 to 19.5 mEq/liter), the P_{CO_2} decreased (33.4 to 27.5 mm Hg), and the pH increased (7.42 to 7.48). Plasma acetate slowly increased during dialysis (0.06 to 5.3 mM). Although during hemodialysis there was a slight fall in blood bicarbonate, after the end of dialysis the acetate that had accumulated was rapidly metabolized, and bicarbonate rebounded above predialysis concentrations and towards normal. The blood P_{CO_2} also increased, and the parallel increase of P_{CO_2} and bicarbonate maintained the pH in an alkaline range. Hemodialysis with acetate as a buffer thus corrects the base deficit of patients with renal failure, but does so only after the treatment has ended.

The acetate and acid-base changes in children were similar in character to the changes described in adult patients receiving 40 mM acetate dialysate and using large surface area dialyzers (2.5 m^2) [3]. There were, however, two important differences between the adults and the children. The adults ended dialysis with a plasma acetate concentration of 10 mM, almost double that of the children, and the fall in blood bicarbonate during dialysis was 4 mEq/liter in the adults and only 0.5 mEq/liter in the children. These differences could be explained either by a more efficient dialysis in the adult patients, or by a greater capacity to metabolize acetate by the children. Because the efficiency of dialysis, as measured by the mass transfer rate of acetate, was greater in children (4.8 mmoles/kg/hour) than it was in adults (3.6 mmoles/kg/hour [3]), we would conclude that children have a greater capacity to metabolize acetate, when corrected for body weight, than do adults. This is probably due to the fact that the metabolically active internal organs comprise a larger percentage of body weight in children [12].

One important goal of dialysis is to supply enough base to the patient to correct the acidosis of renal failure. The base gain of the patient equals the acetate gained minus the loss of bicarbonate and organic acids. The organic acids are important because, like acetate, they consume a hydrogen ion when metabolized, thus functioning as potential base. If the loss of organic acids is not considered, the base balance will be overestimated by 25 to 30%. Some of this loss is occasioned by a 50% increase in plasma concentration of organic acids during and after dialysis, similar to the findings of Tolchin et al [3]. The increase may be due to the load of acetate the patient receives that must be metabolized through conversion to acetyl-CoA. When large quantities of acetyl-CoA are formed, some may be diverted to organic acids; in addition, the conversion of pyruvate, formed from glucose, to acetyl-CoA may be inhibited, resulting in the formation of lactate and other organic acids. The fact that our dialysate contained no glucose may also contribute to the increase of organic acids, because glucose lost to the dialysate may produce a type of starvation ketosis. The exact mechanism of this increase in organic acids remains unresolved.

The balance of base equivalents during hemodialysis indicates that the children received a potential base of 2.1 mEq/kg/day. Because the estimated acid production (without a known source of base loss) is between 1 and 3 mEq/kg/day [13, 14], hemodialysis with sodium acetate should supply the needed base. Prior to dialysis, however, the children had a compensated metabolic acidosis (pH, 7.42; P_{CO_2}, 33.4 mm Hg; and bicarbonate, 20.3 mEq/liter), a finding also observed in adults [15].

The reasons for this acidosis in the presence of what seems to be adequate base delivery during hemodialysis is unclear. There are several possible explanations: *(1)* Some of the children may have lost

Table 4. Comparison of the effects of high efficiency and routine efficiency hemodialysis[a]

	Patient information before dialysis						Dialysis efficiency		
	Age *yrs*	Weight *kg*	pH	ΔP_{CO_2} *mm Hg*	HCO_3^- *mM*	Acetate $t^1/_2$ *min*	C_{Urea} *ml/min/kg*	D_{Ac} *ml/min/kg*	Q_F *ml/hr/kg*
High ($N = 5$)	11.4 ±0.9	33.5 ±3.7	7.43 ±0.01	33.8 ±0.9	21.7 ±0.3	10.0 ±1.4	3.28 ±0.10	2.75 ±0.19	4.8 ±1.2
Routine ($N = 6$)	12.0 ±1.2	39.8 ±8.9	7.40 ±0.02	33.1 ±0.7	19.4 ±0.7	7.6 ±1.1	2.45[d] ±0.23	1.92[c] ±0.26	6.2 ±2.1

[a] Values represent the means ± SEM. Q_F is ultrafiltration flow rate; D_{Ac} is acetate dialysance.
[b] Δ indicates change occurring during hemodialysis. Rebound indicates change occurring in the hour after dialysis.
[c] High efficiency significantly greater than routine efficiency, $P < 0.05$.
[d] High efficiency significantly greater than routine efficiency, $P < 0.01$.

bicarbonate in their urine (although this was not evaluated in our patients, only 3 of 8 had significant urine output). *(2)* Some children were studied during their initial month of dialysis when there may be a greater need to replenish bone buffer. *(3)* Children on hemodialysis may have a greater base need than has been estimated in the past. For a fuller definition of acid-base balance of children undergoing hemodialysis, a more exact and long-term base balance study is needed, where urine and stool base loss, dietary acid intake, and changes in bone content are also evaluated.

Although our results suggest that, in general, acetate is an adequate buffer for children undergoing hemodialysis, they also suggest that with higher efficiency dialysis the children have greater acid-base and acetate changes during and after dialysis, which may be undesireable. The two factors that control acid-base and acetate changes during dialysis are the patient's ability to metabolize acetate and the efficiency of dialysis. When we compared high efficiency and routine efficiency dialysis, children in the high-efficiency group had a greater decrease in P_{CO_2} during dialysis, which can probably be explained by increased removal of total carbon dioxide during dialysis [16] or possibly by a respiratory change [17]. They also had a decrease in blood bicarbonate and a large increase in plasma acetate throughout the 4 hours of dialysis, whereas the children in the routine efficiency group had an increase in bicarbonate and a moderate increase in acetate, most of which occurred during the first hour of dialysis. Thus, children in the high-efficiency group received acetate and lost bicarbonate at a rate exceeding their metabolic ability to generate bicarbonate from acetate. Therefore, even though children have a greater ability (per kilogram of body weight) to metabolize acetate than adults, hemodialysis may still be too efficient, which results in worsening of metabolic acidosis and the accumulation of acetate during dialysis.

The metabolic consequences of high-efficiency dialysis may have accounted for the slightly greater occurrence of hypotensive episodes, nausea, and vomiting in the children of this group. The problems associated with high-efficiency dialysis when acetate dialysate is used have been investigated in adults [4]. In this study, patients undergoing hemodialysis with large-surface-area dialyzers were compared by the use of either acetate dialysate or bicarbonate dialysate, which would eliminate the decrease in bicarbonate and the accumulation of acetate described with acetate dialysate. The same patients, undergoing dialysis with similar efficiency conditions, had a significantly lower incidence of nausea, vomiting, headache, fatigue, and hypotension after bicarbonate replaced acetate in the dialysate. In other studies, high levels of acetate have been associated with cardiovascular instability [18, 19], and rapid changes in bicarbonate have been associated with central nervous system disequilibrium [20, 21]. Although the clinical problems associated with hemodialysis stem from many causes, certain metabolic problems can clearly be attributed to high-efficiency hemodialysis when an acetate dialysate is used. Therefore, we would suggest that dialysis with a urea clearance of greater than 3 ml/min/kg may be harmful in children and should be avoided.

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Table 4. *(continued)*

Acid-base and acetate changes during and after dialysis[b]							Balance of base equivalents			Clinical problems *no. of episodes/ dialysis session*		
Δ pH	Rebound pH	ΔP_{CO_2} *mm Hg*	Rebound P_{CO_2} *mm Hg*	HCO_3 *mM*	Rebound HCO_3 *mM*	End acetate *mM*	Acetate gain *mmoles/kg*	Δ HCO_3^- lost *mmoles/kg*	Potential base *mmoles/kg*	Hypotension	Vomiting	Nausea
0.06 ±0.03	0.00 ±0.02	−8.7 ±2.0	8.0 ±1.4	−3.2[c] ±1.1	5.9 ±1.0	7.50 ±0.86	21.5 ±1.6	14.5 ±0.4	5.0 ±1.8	1.4 ±0.9	0.4 ±0.4	1.6 ±1.0
0.06 ±0.01	0.00 ±0.01	−3.6[c] ±0.8	3.1[c] ±1.1	1.0[c] ±0.8	2.2[c] ±0.7	3.51[d] ±0.55	17.2 ±1.8	11.1[c] ±1.3	4.8 ±0.9	1.0 ±0.5	0.0 ±0.0	0.7 ±0.3

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