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Hemodialysate composition and intradialytic metabolic, acid–base and potassium changes

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Hemodialysate composition and intradialytic metabolic, acid–base and potassium changes. We compared the effects of dialysate composition on changes in intermediary metabolites, acid–base balance, and potassium removal during hemodialysis. Patients were dialyzed against dialysates containing acetate or bicarbonate, each with or without glucose, in a four–way cross–over study. Dialysates containing acetate were associated with significant perturbations in intermediary metabolism, including increases in blood citrate, acetoacetate and β-hydroxybutyrate and a decrease in pyruvate. In contrast, bicarbonate–containing dialysates caused minimal perturbations in intermediary metabolism. Addition of glucose to the dialysate decreased the changes in intermediary metabolites; however, the magnitude of this effect was less than that observed for the change from acetate to bicarbonate. Use of acetate also resulted in lower post–dialysis blood–concentrations of base equivalents than obtained with bicarbonate; this difference was unaffected by the presence or absence of glucose. Although pre- and post-dialysis potassium concentrations were unaffected by the dialysate formulation, total potassium removal was significantly greater when glucose was omitted from the dialysate. Our results suggest that both bicarbonate and glucose should be included in the dialysate, particularly for those patients whose capacity for metabolism may be limited because of highly efficient dialysis, intercurrent illness, or starvation. However, addition of glucose to the dialysate may require a reduction in dialysate potassium to maintain proper potassium homeostasis.

One of the more significant changes in the practice of hemodialysis in recent years has been the revival of interest in using bicarbonate as the base repletion agent in hemodialysate. Although bicarbonate was used historically for base repletion, it was almost completely replaced by acetate after the effectiveness and superior physico-chemical properties of the latter were demonstrated by Mion et al in 1964 [1]. In the late 1970s, questions began to arise regarding possible deleterious hemodynamic effects of acetate and its replacement with bicarbonate was observed to ameliorate adverse symptomatology during dialysis [2]. However, other studies have failed to show any benefit of bicarbonate over acetate with respect to hemodynamic stability, and this remains a controversial issue [3, 4]. Bicarbonate may also be a superior base repletion agent to acetate from a metabolic point of view. Acetate has been shown to perturb intermediary metabolism in both infusion studies [5, 6] and during dialysis against acetate–containing dialysates [7–9]. Such perturbations may impact adversely on base repletion during dialysis. Intermediary metabolites generated subsequent to the metabolism of acetate, including acetoacetate and β-hydroxybutyrate, are dialyzed from the blood, resulting in a loss of 'potential' base. Interpretation of some of these studies is complicated by the use of glucose–free dialysate, since omission of glucose from the acetate–containing dialysate has been shown to perturb intermediary metabolism [9].

Changes in acid–base balance and insulin affect the intrabody distribution of potassium. Potassium can be induced to move from the extracellular to the intracellular space by increasing blood pH [10] or plasma insulin concentration [11], while decreasing blood pH [10] or inhibiting insulin secretion [12] results in the opposite effect. Consequently, the nature of acid–base changes, as well as any changes in plasma insulin secondary to including or excluding glucose from the dialysate, may impact on the ability of dialysis to maintain potassium homeostasis.

The present study sought to clarify these issues by examining the relative impact of the choice of base repletion agent and the presence or absence of glucose in the dialysate on intermediary metabolism, acid–base balance and potassium removal during hemodialysis in a four–way cross–over study.

Methods

Patients

Twelve clinically–stable patients (seven male and five female) were studied. They ranged in age from 30 to 63 years (mean 48 years) and had been maintained on hemodialysis a mean of 27.6 months (range 2 to 54 months). The etiology of their renal failure varied and included hypertensive nephrosclerosis (4 patients), diabetic glomerulosclerosis (4 patients), glomerulonephritis (2 patients) and pyelonephritis (2 patients). The patients took a variety of medications including vitamin supplements, oral phosphate binders and antihypertensive agents; however, drugs, such as sodium bicarbonate and Shohl's solution, known to influence acid–base status were discontinued for the period of the study. Of the four patients with diabetic glomerulosclerosis, two required no hypoglycemic agents while two received NPH insulin daily (12 and 15 IU, respectively). The diabetic patients all conformed to the maturity–onset type. The study was approved by the Human Studies Committee of the University of Louisville and informed consent was obtained from each patient before commencement of the study.

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Hemodialysis procedure

Dialysis was performed for 4.5 hours, three times per week using dialyzers containing 1.0 m^2 of 11 μm wall thickness, regenerated cellulose hollow–fibers (HF100, Cobe Laboratories, Lakewood, Colorado, USA) and Centry II Rx dialysate delivery systems (Cobe Laboratories). Dialyzers were not reused. Dialysate was prepared from softened, reverse osmosis, carbon filtered water. The dialysate composition varied according to the study protocol and contained sodium (135 mmol/liter), calcium (1.5 mmol/liter), magnesium (0.375 mmol/liter), potassium (2 to 3 mmol/liter, according to patient needs), acetate or bicarbonate (both at 35 mmol/liter), and glucose (0 or 11.1 mmol/liter). The concentrates (Rx 110 and Rx 111, Cobe Laboratories) used to prepare the bicarbonate dialysate contained acetic acid (final dialysate concentration 2 mmol/liter) to create the dialysate buffer system; neither of these concentrates contained any additional sodium acetate. Blood access was either by an arteriovenous fistula, bovine or Gortex heterograft, or a Hemasite (Renal Systems, Minneapolis, Minnesota, USA). Blood flow rates were set at 200 ml/min for all patients throughout the study. Anticoagulation was achieved on an individualized basis using a loading dose and constant infusion of heparin [13].

Study protocol

All patients were dialyzed for one week on each of four dialysate formulations, containing acetate, acetate with glucose, bicarbonate, and bicarbonate with glucose, respectively. The order in which each patient was treated with the four dialysate formulations was randomly assigned. Pre- and post-dialysis measurements of acid–base parameters and intermediary metabolites and dialytic exchange of glucose were obtained on the third dialysis with each dialysate formulation. In eight of the patients, all dialyzed against dialysates containing 2 mmol/liter potassium, dialytic removal of potassium was also determined. For all dialyses during which data were collected, the patients were requested to fast overnight (morning dialyses) or following a light breakfast (afternoon dialyses); no food was ingested during dialysis.

Sample collection and analysis

Pre-dialysis blood samples were obtained from the arterial blood access–line prior to dialysis. At the end of dialysis, the dialysate flow through the dialyzer was halted and the post-dialysis blood sample immediately drawn from the arterial blood line. Dialysis was then terminated in the routine manner. Samples for blood pH and gases were drawn into heparinized syringes, placed on ice, and immediately analyzed using a blood gas analyzer (Model 13-213, Instrumentation Laboratory, Lexington, Massachusetts, USA). Serum bicarbonate concentrations were calculated from pH and pCO_2 using the Henderson–Hasselbalch equation and pK of 6.1. Blood for electrolytes, urea and glucose was collected in heparinized syringes, centrifuged immediately and the plasma stored at −70°C until assayed by routine clinical laboratory methods. Net urea generation rate was calculated by means of a single–pool model for urea kinetics and used to estimate hydrogen ion–generation rate [14]. Plasma acetate was determined enzymatically [15] and plasma immunoreactive insulin by radioimmunoassay (Becton Dickinson, Orangeburg, New York, USA). Blood for intermediary metabolites was deproteinated with cold (4°C) perchloric acid immediately following collection, centrifuged, and the supernatant stored at −70°C until assayed by enzymatic methods for lactate and pyruvate (kits 826-UV and 726-UV, Sigma Chemical Co., St. Louis, Missouri, USA), citrate [16], acetoacetate [17] and β-hydroxybutyrate [18].

The net transfer of glucose and potassium between blood and dialysate was determined by graphically integrating serial determinations of the instantaneous flux of solute, $\dot{m}$, over the time of dialysis. The instantaneous flux is given by:

$$\dot{m} = Q_{Do}C_{Do} - Q_{Di}C_{Di}$$

where Q_D is the dialysate flow rate, C_D is the dialysate concentration, and the subscripts i and o refer to the dialyzer inlet and outlet, respectively. The outlet dialysate flow–rate was measured by timed volumetric collection. The inlet dialysate flow–rate was then determined as the outlet flow rate less the calculated ultrafiltration rate.

Data analysis

Within groups, pre- to post-dialysis changes were evaluated using Student's *t*-test for paired data. Pre-dialysis values were compared between groups by analysis of variance. A two–way analysis of variance [19] was used to separate and compare the effect of acetate versus bicarbonate and the effect of including or excluding glucose on pre- to post-dialysis changes. Changes were considered statistically significant for P values less than 0.05. Values are given as mean ± standard deviation for N observations.

Results

Intradialytic fluid removal was comparable between dialysate formulations, averaging 2.0 kg, overall. Comparison of pre-dialysis solute concentrations revealed no differences from one dialysate formulation to another. Further comparisons showed that, pre-dialysis, the four patients with diabetic glomerulosclerosis differed from the remaining patients in a manner consistent with their diabetes. They had increased plasma glucose concentrations (9.8 ± 3.7 mmol/liter vs. 5.4 ± 0.8 mmol/liter, $P < 0.005$), were slightly more acidemic (pH = 7.323 ± 0.039 vs. 7.379 ± 0.038, $P < 0.01$), and had increased ratios of blood lactate to blood pyruvate (23.0 ± 9.7 vs. 16.7 ± 4.8, $P < 0.05$). However, there were no differences in any of the other parameters measured and pre- to post-dialysis changes induced by dialysis were similar for both diabetic and non-diabetic patients. Accordingly, the patients were treated as a single group in comparing the effects of the four dialysate formulations.

Changes in acid–base parameters

Changes in arterial pH, blood gases, bicarbonate, and hydrogen ion generation rate are indicated by the data in the upper portion of Table 1, while the P values listed in the lower portion of the Table reflect the two–way analysis of variance for these parameters. Also shown in Table 1 are the total pre- and post-dialysis plasma concentrations of the measured organic anions, that is, the sum of the concentrations of bicarbonate,

Table 1. Pre- and post-dialysis blood gas and acid–base parameters

	pH	pCO_2 *mm Hg*	Bicarbonate *mmol/liter*	pO_2 *mm Hg*	Total organic anions *mmol/liter*	Hydrogen ion generation rate *mmol/24 hrs*
Acetate						
Pre-dialysis	7.346 ± 0.035	37.1 ± 3.8	19.7 ± 2.4	100 ± 15	20.83 ± 2.54	57.3 ± 13.8
Post-dialysis	7.409 ± 0.050[a]	30.9 ± 3.5[a]	19.0 ± 2.4	101 ± 16	25.93 ± 2.57[a]	
Acetate + glucose						
Pre-dialysis	7.350 ± 0.052	35.7 ± 3.2	19.6 ± 2.5	100 ± 13	20.88 ± 3.05	50.6 ± 12.7
Post-dialysis	7.417 ± 0.056[a]	30.9 ± 4.7[a]	19.4 ± 2.8	93 ± 13	24.66 ± 3.18[a]	
Bicarbonate						
Pre-dialysis	7.360 ± 0.059	37.7 ± 3.9	21.0 ± 4.0	101 ± 10	22.18 ± 4.10	53.0 ± 12.3
Post-dialysis	7.482 ± 0.052[a]	36.3 ± 3.7	26.6 ± 3.0[a]	97 ± 9[a]	28.71 ± 3.19[a]	
Bicarbonate + glucose						
Pre-dialysis	7.383 ± 0.044	38.1 ± 5.1	22.1 ± 2.9	105 ± 13	23.25 ± 2.82	48.4 ± 13.5
Post-dialysis	7.483 ± 0.059[a]	38.7 ± 4.5	28.2 ± 2.9[a]	103 ± 9	29.74 ± 2.80[a]	
Acetate vs. bicarbonate	$P = 0.0126$	$P = 0.004$	$P = 0.001$	NS	$P = 0.0415$	NS
Glucose vs. glucose–free	NS	NS	NS	NS	NS	NS

Data shown as mean ± SD for $N = 12$
[a] Significantly different from pre-dialysis

Table 2. Pre- and post-dialysis concentrations of electrolytes, glucose and insulin

	Sodium *mmol/liter*	Potassium *mmol/liter*	Chloride *mmol/liter*	Phosphorus *mmol/liter*	Glucose *mmol/liter*	Insulin *mU/liter*
Acetate						
Pre-dialysis	136 ± 4	5.3 ± 1.1	103 ± 4	2.0 ± 0.6	6.3 ± 1.9	24 ± 25
Post-dialysis	135 ± 3	3.7 ± 0.4[a]	99 ± 3[a]	1.1 ± 0.2[a]	4.9 ± 1.2[a]	13 ± 6
Acetate + glucose						
Pre-dialysis	136 ± 4	5.0 ± 0.8	103 ± 5	2.0 ± 0.5	7.0 ± 3.1	23 ± 14
Post-dialysis	135 ± 3[a]	3.5 ± 0.3[a]	99 ± 3[a]	1.1 ± 0.2[a]	6.6 ± 2.1	23 ± 12
Bicarbonate						
Pre-dialysis	137 ± 4	5.1 ± 1.1	102 ± 5	2.1 ± 0.7	7.1 ± 3.7	27 ± 23
Post-dialysis	135 ± 4	3.7 ± 0.4[a]	95 ± 3[a]	1.1 ± 0.2[a]	5.2 ± 1.3[a]	14 ± 9[a]
Bicarbonate + glucose						
Pre-dialysis	137 ± 4	5.2 ± 1.0	101 ± 5	1.9 ± 0.4	7.1 ± 3.4	19 ± 10
Post-dialysis	136 ± 4	3.7 ± 0.5[a]	96 ± 3[a]	1.0 ± 0.2[a]	6.8 ± 2.4	22 ± 15
Acetate vs. bicarbonate	NS	NS	NS	NS	NS	NS
Glucose vs. glucose–free	NS	NS	NS	NS	$P = 0.0400$	$P = 0.0094$

Data shown as mean ± SD for $N = 12$
[a] Significantly different from pre-dialysis

acetate, lactate, pyruvate, citrate, acetoacetate and β-hydroxybutyrate. Changes in this value indicate the gain in base as 'potential' bicarbonate in addition to bicarbonate, per se. All four dialysate formulations resulted in net base gain by the patient during dialysis. However, bicarbonate was superior in this regard as evidenced by significantly greater increases in pH, bicarbonate, and total organic anions. The addition of glucose had no impact on changes in acid–base parameters with either dialysate.

Changes in electrolytes, glucose and insulin

Table 2 presents pre- and post-dialysis concentrations of sodium, potassium, chloride, phosphorus, glucose, and insulin. Plasma concentrations of potassium, phosphorus, and chloride were significantly decreased by dialysis; however, this decrease was not influenced by the choice of base repletion agent or whether or not glucose was included in the dialysate. Omission of glucose from the dialysate resulted in a loss of 30.0 ± 9.2 g of glucose by the patient and caused statistically significant decreases in plasma glucose and insulin in comparison to the use of glucose–containing dialysate which produced an uptake of 15.8 ± 12.2 g of glucose by the patient ($P = 0.0001$ compared with glucose–free). Net glucose transfer and changes in glucose and insulin were unaffected by the choice of acetate or bicarbonate.

The data in Table 3 show the effect of dialysate composition on dialytic potassium removal in the group of eight patients in which these measurements were made. While pre- and post-dialysis plasma potassium concentrations were unaffected by the dialysate used, the total amount of potassium removed by dialysis did vary. Substantially more potassium was removed during those treatments in which glucose was omitted from the

Table 3. Dialytic removal of potassium, and glucose, pre- and post-dialysis plasma potassium, glucose and insulin, and pre- and post-dialysis pH in a subgroup of eight patients

	Potassium removal *mmol*		Plasma potassium *mmol/liter*	Glucose removal *g*	Plasma glucose *mmol/liter*	Plasma insulin *mU/liter*	pH
	Total	Intracellular					
Acetate							
Pre-dialysis	79.7 ± 20.5	57.2 ± 16.7	5.0 ± 0.7	27.7 ± 5.0	5.9 ± 1.3	28 ± 30	7.365 ± 0.018
Post-dialysis			3.6 ± 0.3[a]		5.1 ± 1.3	12 ± 5	7.432 ± 0.035[a]
Acetate + glucose							
Pre-dialysis	62.2 ± 19.3	37.3 ± 15.3	4.9 ± 0.6	−18.2 ± 5.9	5.7 ± 1.7	24 ± 12	7.367 ± 0.027
Post-dialysis			3.4 ± 0.2[a]		5.7 ± 1.3	22 ± 8	7.441 ± 0.045[a]
Bicarbonate							
Pre-dialysis	72.0 ± 26.4	48.4 ± 20.1	4.8 ± 1.1	29.3 ± 5.0	6.7 ± 2.7	30 ± 26	7.389 ± 0.050
Post-dialysis			3.5 ± 0.2[a]		4.7 ± 0.7	15 ± 8	7.503 ± 0.042[a]
Bicarbonate + glucose							
Pre-dialysis	54.5 ± 24.1	26.5 ± 14.8	5.3 ± 1.0	−20.6 ± 13.7	6.0 ± 2.2	19 ± 7	7.391 ± 0.048
Post-dialysis			3.5 ± 0.3[a]		5.8 ± 1.3	23 ± 17	7.516 ± 0.037[a]
Acetate vs. bicarbonate	NS	NS	NS	NS	NS	NS	$P = 0.0431$
Glucose vs. glucose–free	$P = 0.0358$	$P = 0.0019$	NS	$P = 0.0001$	$P = 0.0387$	$P = 0.0219$	NS

Data shown as mean ± SD for $N = 8$
[a] Significantly different from pre-dialysis

Table 4. Pre- and post-dialysis blood concentrations of acetate, lactate, pyruvate, citrate, acetoacetate, and β-hydroxybutyrate

	Acetate *μmol/liter*	Lactate *mmol/liter*	Pyruvate *μmol/liter*	Citrate *μmol/liter*	Acetoacetate *μmol/liter*	β-hydroxybutyrate *μmol/liter*
Acetate						
Pre-dialysis	42 ± 20	0.74 ± 0.20	48 ± 23	97 ± 52	98 ± 78	130 ± 297
Post-dialysis	3603 ± 1742[a]	0.66 ± 0.14	29 ± 12[a]	151 ± 61[a]	691 ± 465[a]	1266 ± 891[a]
Acetate + glucose						
Pre-dialysis	43 ± 22	0.73 ± 0.21	40 ± 16	98 ± 66	108 ± 113	125 ± 319
Post-dialysis	3503 ± 2416[a]	0.63 ± 0.18	28 ± 9[a]	128 ± 43[a]	376 ± 298[a]	638 ± 717[a]
Bicarbonate						
Pre-dialysis	41 ± 17	0.75 ± 0.19	48 ± 23	95 ± 66	116 ± 155	136 ± 347
Post-dialysis	114 ± 45[a]	0.73 ± 0.28	38 ± 20	114 ± 49[a]	378 ± 264[a]	778 ± 761[a]
Bicarbonate + glucose						
Pre-dialysis	59 ± 41	0.84 ± 0.40	49 ± 29	95 ± 54	85 ± 33	56 ± 62
Post-dialysis	99 ± 45[a]	0.70 ± 0.18	34 ± 15	98 ± 42	218 ± 154[a]	359 ± 343
Acetate vs. bicarbonate	$P = 0.0001$	NS	NS	$P = 0.0070$	$P = 0.0096$	$P = 0.0261$
Glucose vs. glucose–free	NS	NS	NS	NS	$P = 0.0113$	$P = 0.0036$

Data shown as mean ± SD for $N = 12$
[a] Significantly different from pre-dialysis

dialysate. Glucose–free treatments were also associated with the dialytic removal of glucose which resulted in decreases in plasma glucose and insulin, relative to treatments with glucose–containing dialysates. Although pre- and post-dialysis pH changes were greater with bicarbonate than with acetate, the choice of base repletion agent did not have a significant impact on potassium removal. The contribution of the intracellular compartment to potassium removal was estimated by using the value for total body water obtained from the urea kinetic analysis [14], assuming 42% of total body water to be intracellular, and taking pre- and post-dialysis plasma potassium concentrations as representative of extracellular concentrations at those times. The values for intracellular potassium removal given in Table 3 were then obtained from a simple mass balance. Depending on the dialysate formulation, 53% to 72% of potassium removed was derived from intracellular stores. Although these values are only approximations because of the assumptions made in the calculations, any errors should be consistent for a given patient, thereby allowing meaningful comparisons to be made between dialysate formulations.

Changes in intermediary metabolites

Pre- and post-dialysis blood concentrations of acetate, lactate, pyruvate, citrate, acetoacetate, and β-hydroxybutyrate are given in the upper portion of Table 4, and the results of the two–way analysis of variance for these parameters in the lower portion. Blood acetate concentrations increased during dialysis with all four dialysate formulations; however, the increase with

acetate–containing dialysates was much greater than that with bicarbonate–containing dialysates. Acetate caused blood citrate concentrations to increase and blood pyruvate concentrations to decrease significantly; these changes were reduced by substituting bicarbonate for acetate. Blood lactate concentrations were unaffected by the dialysate composition. All dialysate formulations caused some increase in the blood concentrations of acetoacetate and β-hydroxybutyrate. These changes were greatest with acetate in the absence of glucose, while they were minimized by the combination of bicarbonate and glucose.

Discussion

The data obtained in this study allow two different stimuli to intermediary metabolism, infusion of acetate and removal of glucose, to be compared and contrasted in the circumstance of dialysis. When acetate is used in the dialysate, buffer repletion relies on generation of bicarbonate secondary to metabolism of acetate through complex metabolic pathways, including the Krebs cycle and oxidative phosphorylation [20]. This involvement of the Krebs cycle is reflected in the increased blood citrate concentrations seen with dialysis against acetate–containing dialysates (Table 4). The first step in acetate metabolism is the formation of acetyl coenzyme A. As long as sufficient oxaloacetate is available for acetylation to citrate, acetate will enter the Krebs cycle and be metabolized to carbon dioxide and water. Increased concentrations of acetyl coenzyme A are known to induce synthesis of oxaloacetate from pyruvate through pyruvate carboxylase [21] and the decrease in blood pyruvate concentrations seen with acetate–containing dialysates may reflect this process. However, if these pathways become overloaded, acetyl coenzyme A will be diverted into production of acetoacetate and β-hydroxybutyrate. Indeed, the increases in acetoacetate and β-hydroxybutyrate seen in this and other studies [7–9] suggest that the capacity of the Krebs cycle to metabolize acetate is exceeded during dialysis. We have previously reported [6, 22] similar changes in citrate, pyruvate, acetoacetate, and β-hydroxybutyrate in studies in which acetate was infused in the absence of dialysis, suggesting that these changes reflect acetate metabolism, per se, and are not merely a consequence of the dialytic process.

Dialytic removal of glucose can also induce changes in intermediary metabolism. It has been estimated [9] that removal of quantities of glucose similar to those found with glucose–free dialysates in this study (25 to 35 g) will stimulate glycogenolysis and gluconeogenesis. The relative role of these two processes in replacing glucose losses will depend on body glycogen stores. In non-fasting patients glycogen stores will be appreciable; whereas, with fasting, glycogen stores will decrease and gluconeogenesis will become progressively more dominant in sustaining blood glucose levels. The patients in this study fasted 6 to 12 hours and could be expected to have reduced glycogen stores. Gluconeogenesis from lactate involves the conversion of pyruvate to oxaloacetate; this oxaloacetate is phosphorylated to phospho-enol-pyruvate and, thence, via the Embden–Meyerhof pathway to glucose. Decreases in blood pyruvate [9, 23] and alanine [23] during dialysis against glucose–free, acetate–containing dialysates have been taken as evidence of increased gluconeogenesis during dialysis. The observation that plasma glucose decreases but assumes a new steady state level early in dialysis with glucose–free dialysate [9] is also suggestive that glucose is derived from either glycogenolysis or gluconeogenesis, or both. However, as discussed previously, blood pyruvate may decrease secondary to acetate metabolism, alone. Although we did not measure blood alanine concentrations in this study, we have previously demonstrated [6, 22] that blood alanine concentrations also decrease during acetate infusion in the absence of dialysis.

Ketone production is also responsive to the glucagon to insulin ratio [24], with an increase in the ratio favoring the formation of acetoacetate and β-hydroxybutyrate. We did not measure glucagon levels in this study as they are difficult to interpret in chronic renal failure because of the presence of an immuno-reactive precursor of questionable biological activity [25]. However, plasma insulin levels decreased when glucose was omitted from the dialysate, suggesting an increase in the glucagon to insulin ratio and enhanced ketogenesis. This mechanism most likely exacerbated acetoacetate and β-hydroxybutyrate formation when acetate was used in the absence of glucose and may also explain the increases seen when bicarbonate was used in the absence of glucose. Small increases in acetate, acetoacetate and β-hydroxybutyrate were observed when bicarbonate was used as the base repletion agent. These changes are most likely caused by the 2 mmol/liter acetic acid included in the dialysate to buffer the bicarbonate, rather than an effect of bicarbonate, per se.

Consequently, the dialytic loss of glucose and the influx of acetate might be expected to compete for pyruvate, the combination of the two maximally perturbing intermediary metabolism. The data in Table 4 support this contention and show further that, of the two stimuli, acetate has the more profound effect on intermediary metabolism. In comparison to bicarbonate, use of acetate as the base repletion agent caused significantly greater increases in blood levels of acetate, citrate, acetoacetate, and β-hydroxybutyrate. Omission of glucose from the dialysate exacerbated the increases in acetoacetate and β-hydroxybutyrate, so that the greatest changes in intermediary metabolism were observed with the use of glucose free, acetate–containing dialysate and the smallest changes with the use of dialysate containing both bicarbonate and glucose. The effect of adding glucose to the dialysate is in general agreement with previous studies [9, 26], although we did not observe the decrease in post-dialysis acetate concentration, relative to glucose–free dialysate, described by Desch et al [26] for acetate–containing dialysates.

Replenishment of bicarbonate buffer stores depleted by inter-dialytic acid generation is an important goal of dialysis therapy. The organic anions which accumulate in the blood during acetate dialysis represent "potential" bicarbonate and are removed from the blood by dialysis. At the same time, bicarbonate is also lost into the dialysate so that the net accrual of base by the patient is a balance between the uptake of acetate and the loss of bicarbonate and organic anions. It has been speculated [27] that the net accrual of base with acetate dialysis may be insufficient to meet the goal of neutralizing inter-dialytic acid production and that this may lead to chronic depletion of body buffer stores, such as those of bone. Although this concept remains controversial, it is true that many patients present for dialysis with a marked metabolic acidosis so that maximizing net base accrual is an important objective. The data in Table 1 show that substitution of bicarbonate for acetate as

the base repletion agent has a significant impact on base repletion as judged by changes in blood pH and blood levels of bicarbonate and total organic anions. It is important to consider total organic anions when interpreting the data obtained with acetate containing dialysates, as accumulated non-bicarbonate organic anions will be metabolized to bicarbonate once dialysis ceases. Including glucose in the dialysate has the further, albeit relatively minor, effect of reducing blood concentrations and, hence, dialytic loss of acetoacetate and β-hydroxybutyrate.

Although the increase in total organic anions during dialysis in this study was only 1 to 2 mmol/liter greater with bicarbonate–containing dialysates than with acetate–containing dialysates (Table 1), the cumulative effect on body buffer stores over months of dialysis may be significant. The impact may be more profound in some therapies, such as high efficiency, short time dialysis. While net acid production remains unchanged, these therapies require that base repletion must be carried out in a much shorter time and, therefore, at higher rates of mass transfer. In the circumstance of dialysis against acetate, the bidirectional fluxes of acetate and bicarbonate will be increased leading to increased generation and dialytic loss of acetoacetate and β-hydroxybutyrate. This may serve to further compromise base repletion. The concept of shortening dialysis time by increasing dialyzer performance was first proposed by Babb et al in 1972 [28] and several clinical evaluations were performed in the mid-1970s [29–31]. Although acid–base data were not always presented in these reports, two prospective, cross–over studies [30, 31] showed pre-dialysis serum bicarbonate concentrations to be decreased during the period of short time dialysis. The concept of short time dialysis has recently been revived [32]. In comparison to earlier studies, both the efficiency of the dialyzers and the blood flow rates now being used are increased and an even more profound effect on base repletion might be expected. For this reason, it would seem prudent to use bicarbonate–containing dialysates for these therapies. Indeed, it has been suggested [33] that the use of bicarbonate is a requirement for adequate acid–base balance in high efficiency, short time dialysis as practiced today. The additional inclusion of glucose in the dialysate would also seem warranted, particularly in patients who may have limited hepatic glycogen stores.

The presence or absence of glucose in the dialysate also influenced dialytic potassium removal (Table 3), with potassium removal being greater when glucose was omitted from the dialysate. Changes in plasma insulin are known to effect redistribution of potassium; inhibition of insulin secretion causes movement of potassium into the extracellular space [12], while insulin infusion has the opposite effect [11]. These mechanisms continue to operate in maturity onset diabetics with normal insulin levels [12], as was the case with the diabetic patients in this study. Omission of glucose from the dialysate resulted in decreased plasma insulin–concentrations (Table 2), which in turn would enhance egress of potassium from cells and maximize the potassium available for dialytic removal. That the additional potassium removed did derive from intracellular stores is further supported by the observation that pre- to post-dialysis changes in plasma potassium did not differ from one dialysate formulation to another. Accordingly, changes in plasma concentrations are a poor guide to dialytic removal of potassium and maintenance of proper potassium homeostasis may depend on selecting an appropriate dialysate concentration of both glucose and potassium. Changes in acid–base status can also affect the intracorporeal distribution of potassium [10], with an increase in pH favoring an intracellular shift of potassium. Use of bicarbonate in the dialysate resulted in significantly greater increases in blood pH than were obtained with acetate (Table 1). However, although there was a tendency for potassium removal to be less with bicarbonate, the choice of base repletion agent did not have a statistically significant impact on potassium removal. This is in general agreement with previous work by Williams et al [34]. Cases of severe hypokalemia during hemodialysis have been ascribed to dialytic correction of acidosis [35]; however, the changes in blood pH in these cases were much greater than observed in our patients.

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