The effect of changing dialysate bicarbonate concentration on serum bicarbonate, body weight and normalised nitrogen appearance rate

Abstract

Introduction

Most haemodialysis machines deliver a fixed bicarbonate concentration. Higher concentrations may improve acidosis, but risk post-haemodialysis alkalosis, whereas lower concentrations potentially increase acidosis but reduce alkalosis. We reviewed the effects of lowering dialysate bicarbonate.

Methods

We reviewed peri-dialysis chemistries in patients switching to a lower bicarbonate dialysate at 4 time points over 19 months.

Results

We studied 126 patients, mean age 63.7±16.3 years, 57.9% males. Post-haemodialysis alkalosis fell from 1.6 to 0.3% sessions, but pre-haemodialysis acidosis increased from 11.9 to 23.8% sessions (p=0.005) reducing dialysate bicarbonate from 32 to 28 mmol/L. After 3 months, pre-haemodialysis serum bicarbonate fell (21.1±2.3 to 19.8±2.2 mmol/L), and post-haemodialysis (24.9±2.1 to 22.5±2.0 mmol/L, p<0.001 with a fall

in pre-haemodialysis weight from 74.6±20.7 to 71.7±18.2 kg, normalised protein nitrogen accumulation rate 0.8±0.28 to 0.77±0.2 g/kg/day, p<0.05, and serum albumin 39.7±4.2 to 37.7±4.9 g/L, p<0.001. Thereafter, apart from pre- and post-haemodialysis serum bicarbonate, weight and normalised protein nitrogen accumulation stabilised, although albumin remained lower (37.6±4.0 g/L, p<0.001). On multivariate logistic analysis, serum bicarbonate increased more with lower pre-haemodialysis bicarbonate standardised coefficient β 0.5 (95% confidence interval -0.6 to -0.42), increased normalised protein nitrogen accumulation β 0.2 (0.96 to 2.38), p<0.001, and session time β 0.09, (0.47to 5.98), p<0.022, and less with lower dialysate bicarbonate 0-.23 (-1.54 to -0.74), p<0.001.

Conclusion

Increases in SE-Bic with haemodialysis, depend on the bicarbonate gradient, session time and nPNA. Lower D-Bic reduces post-haemodialysis alkalosis but increases pre-haemodialysis acidosis and may initially have adverse effects on weight and normalised protein nitrogen accumulation.

Abbreviations

CKD chronic kidney disease

CKD-MBD – chronic kidney disease metabolic bone disease

HD haemodialysis

Kt/V dialyser urea clearance

nPNA normalised protein nitrogen accumulation

PTH parathyroid

VIF variable inflation factor

X2 Chi square

UK United Kingdom

Introduction

Patients with progressive chronic kidney (CKD) disease develop a metabolic acidosis, which if untreated increases progression of CKD [1], reduces dietary protein intake, and increases risk of sarcopenia [2] and CKD metabolic bone disease (CKD-MBD), as bicarbonate is released from bone in an attempt to compensate for the acidosis [3]. As such, correction of metabolic acidosis is one of the key objectives of dialysis treatments. Over time, bicarbonate has replaced acetate and lactate as the main source of anionic base in dialysis fluids.

Most haemodialysis (HD) machines can only deliver a fixed dialysate bicarbonate, and there has been debate as to the optimum bicarbonate concentration. Observational studies have reported increased mortality for patients with both low and high pre-dialysis serum bicarbonate concentrations [4]. Although there are interventional prospective studies reporting that using higher bicarbonate dialysates leads to increased dietary intake and body weight [5,6], there are also observational reports demonstrating an association with increased mortality [7] and sudden death [8]. Higher bicarbonate dialysates have also been reported to affect calcium mass balance, and potentially increase the risk of vascular calcification compared to lower concentrations over the longer term [9].

International and national clinical guideline committees have variously suggested that pre-midweek dialysis serum bicarbonate, measured as total CO_2, should be between 19 and 26 mmol/L, and some have also included a post-dialysis target of ≤29 mmol/L [10,11,12]. However, whereas there are recommendations for other components of the dialysate, committees have avoided advising on dialysate bicarbonate concentrations [13].

Due to concerns over risks of vascular calcification we reduced the delivered bicarbonate concentration from 32 mmol/L to 28 mmol/L and

report on the changes in pre- and post-dialysis serum bicarbonate and patient weight over 18 months.

Patients and Methods

In March 2020, the dialysate delivered to patients was changed from a bicarbonate of 32 mmol/L and acetate of 3 mmol/L to one of a bicarbonate of 28 mmol/L and acetate of 3 mmol/L. Serum bicarbonate was not measured with every set of monthly blood tests, but in November 2019, and then May and July 2020, and May and September 2021. Serum bicarbonate was measured as total CO_2, albumin by bromocresol green method and C reactive protein, parathyroid hormone (PTH) and haemoglobin by standard methods (Roche Cobas, Roche Diagnostics Ltd, Burgess Hill, United Kingdom (UK), Haematology systems, Sysmex Corporation, Milton Keynes, UK [14,15]). Patients were dialysed with Fresenius 4008 and 5008 dialysis machines and high flux polysulfone dialysers (Fresenius Medical Company, Bad Homberg, Germany) [16], which were regularly calibrated using conductivity standards [17]. All sessions using ultrapure dialysis quality water and single bolus low molecular weight heparin was used for anticoagulation [18]. Dialyser urea clearance (Kt/V) was calculated along with normalised nitrogen appearance rate using standard methods [11]. Lean body mass was

estimated by calculating the creatinine index [19], and then lean tissue index [19].

Statistical analysis

Results are expressed as mean ± standard deviation, or median and interquartile range, or percentage. Standard statistical analyses were used: D'Agostino & Pearson normality test, Chi square (X2), paired t test, Wilcoxon rank sum test, anova or Kruskal-Wallis tests with appropriate post-hoc Bonferroni or Games-Howell correction. Univariate analysis was undertaken by Pearson or Spearman correlation and followed by a multivariable linear model including all variables with an initial univariate association of <0.1, and then variables were excluded in a step-backward model if they were not significant, unless the improved model fit. The model was checked for collinearity and variable inflation factor (VIF). Statistical analysis was performed using Graph Pad Prism (version 9.2, Graph Pad, San Diego, CA, USA), Statistical Package for Social Science version 28.0 (IBM Corporation, Armonk, New York, USA). Statistical significance was taken at or below the 5% level.

Ethics

This audit of a change in clinical practice complied with UK National Research Ethical standards (NRES) for clinical practice development and audit and did not require formal NRES committee approval. All data collected was appropriately anonymised.

Results

126 patients dialysed against a dialysate bicarbonate of 32 and then 28 mmol/L (Figure 1), with peri-dialysis bicarbonate measured during 517 dialysis sessions; 391 with a bicarbonate of 28 mmol/L and 126 with 32 mmol/L. During the nineteen months of follow-up a total of 42 patients died as a consequence of COVID-19 infection, predominantly during the first wave of the original COVID-19 strain, and then later from the alpha and delta strains, as vaccination only became available in February and March 2021. As expected there a significant univariate correlation between the pre-dialysis bicarbonate concentration and increase in serum bicarbonate with dialysis (Figure 2) and the dialysate to serum gradient and increase in serum bicarbonate (Figure 3).

We then reviewed the effect of changing from a dialysate bicarbonate of 32 to 28 mmol/L in a single dialysis centre (Table 1). After lowering the dialysate bicarbonate concentration pre- and post-dialysis serum bicarbonate measurements were lower at all time points. On the

first assessment, 2 months after instituting the change, then along with a smaller increase in serum bicarbonate, patient pre-dialysis weight was lower, as was estimated dietary protein intake, serum albumin (Table 1). However, estimates of lean body mass, creatinine index and lean tissue index did not change after 2 months, then increased after 4 months, and then stabilised. Similarly, with time, apart from increasing patient age, there were few differences apart from the serum bicarbonate values.

To determine whether there was an effect of the duration of the dialysis session, we compared patients dialysing for 180, 210 and 240 minutes, patients with different dialysis session times being excluded from analysis. (Table 2). Serum bicarbonate both pre- and post-dialysis were lower for patients dialysing with 28 mmol/L bicarbonate. The change in bicarbonate was only significantly different for those dialysing for 210 minutes.

The increase in serum bicarbonate following dialysis was associated with nPNA, serum creatinine, albumin, and negatively with pre-dialysis bicarbonate and age (Table 3). In a multivariable model, only nPNA and session duration remained independently associated with the change in serum bicarbonate, and negatively with pre-dialysis bicarbonate (Table 4).

The post-dialysis serum bicarbonate was ≥29 mmol/L in 1.6% of dialysis sessions with a bicarbonate of 32 mmol/L and 0.3% of sessions

with a bicarbonate of 28 mmol/L (X2 2.9, p=0.09). The pre-dialysis serum bicarbonate was < 19 mmol/L prior to 11.9% of sessions with a dialysate of 32 and 23.8% of those with a dialysate of 28, X2 10.6, p=0.005. A pre dialysis bicarbonate of < 19 mmol/L was more common with dialysis sessions of < 3 hours (21.4%) compared to 3 hours (19.1%), 3.5 hours (22.5%) and 4 hours (19.0%), X2 19.9, p=0.011. Patients with a pre-dialysis bicarbonate of < 19, had higher nPNA (0.88±0.20 vs 0.78±0.18 g/kg/day), p<0.001, pre-dialysis serum creatinine (798 (589-1012 vs 700 (543-888) umol/L, p=0.03, and phosphate (1.84 ±0.55 vs 1.71 ±0.5 mmol/L), p=0.05.

Discussion

As the generation of acids depends on nutritional intake, physical activity and body composition, then ideally, dialysate bicarbonate should be individualised [20]. However, very few dialysis machines allow any individualisation, and as such centres have to opt for one concentration for all patients, leading to low pre-HD serum bicarbonate in some patients and overshooting post-HD in others. Prior to switching to a lower dialysate bicarbonate dialysate, we had almost 12% of sessions with patients starting HD with a low serum bicarbonate and 1.6% overshooting post HD. Due to concerns over a potential positive calcium balance by using a higher bicarbonate dialysate [21], we changed from a combination

of 32 mmol/L bicarbonate and 3 mmol/L acetate to 28 mmol/L bicarbonate and 3 mmol/L acetate.

We followed a cohort of 126 patients who had at least one or more measurements of pre- and post-HD serum bicarbonate using both dialysate compositions. There was strong association between the increase in serum bicarbonate post-HD and the dialysate to serum gradient. Compared to previous short-term studies we followed patients for just over 18 months. After 3 months patients had lost weight, associated with a reduction in estimated dietary protein intake as assessed by nPNA, pre-dialysis serum albumin and creatinine, with no change in dialysis session times, Kt/V or ultrafiltration volumes. The lower pre-HD bicarbonate led to an absolute greater increase in bicarbonate with HD. The changes in weight and diet would be in keeping with reports of the catabolic effect of acidosis contributes on muscle wasting and malnutrition of HD patients [22]. Acidosis also potentially increases bicarbonate release from bone [23], with reports of correcting acidosis reducing parathyroid hormone (PTH) levels [24]. However, we found no effect on PTH following the change in dialysate bicarbonate, however reports from other studies have varied with both increased and decreased PTH observed [20,21]. However, a few months later although pre-HD bicarbonate remained lower, there were now no differences in

weight, nPNA, serum albumin or creatinine. Sessional weight loss was less and haemoglobin higher. The first pandemic wave of COVID-19 came in early March 2020 [25], and as such some of the weight loss, reduced nPNA and serum creatinine observed in May 2020 may have additionally been due to COVID-19 infections, government lockdowns and restrictions on leaving the house and social activities, then followed by some improvement as COVID-19 infections decreased. This potential effect of COVID-19 would be supported by no apparent reduction in estimates of lean body mass [19] after 2 months of using the lower bicarbonate dialysate. Although later review after 15 and 19 months showed that the serum albumin remained lower with the lower dialysate bicarbonate, albeit estimates of lean body mass did not differ.

Comparing dialysis sessions of different duration, then patients using the lower dialysate bicarbonate had lower pre- and post-HD serum bicarbonate values whether they dialysed for 3.0,3.5- or 4.0-hour sessions. Bicarbonate transfer from the dialysate depends on the gradient between dialysate and plasma, which falls during the first phase of dialysis, and as such longer HD sessions might be expected to result in greater bicarbonate transfer, with greater increase, and higher post-HD bicarbonate [26]. However, bicarbonate is removed from plasma by ultrafiltration and convection [27], and so the greater ultrafiltration with

longer HD sessions may account for finding no differences with the three specified session times.

In keeping with other studies, the change in serum bicarbonate on univariate analysis was associated with factors associated with nutrition and muscle mass [28,29], and dialysis session duration [27]. Whereas a lower gradient and increasing age, presumably due to smaller appetite, less muscle and physical activity led to a smaller increase in serum bicarbonate [30]. Thus, on multivariable analysis the increase in serum bicarbonate was dependent upon nPNA, the gradient between pre-HD serum bicarbonate and dialysate bicarbonate concentration and then duration of HD session.

Changing patients to a lower dialysate bicarbonate reduced post-HD high serum bicarbonate from 1.6 to 0.3% of sessions but increased low pre-HD bicarbonate measurements doubled from around 12 to 24%. However, patients with lower bicarbonate values had higher nPNA and serum creatinine and phosphate, potentially suggesting that this may have been due to increased acid production due to better diet and physical activity [31]. It has to be recognised that low bicarbonate laboratory values may not always reflect metabolic acidosis, as errors in sampling, air retained in blood tubes and delays in measurement can all lead to a lower laboratory result [27,33]. So, despite using vacutainers designed to

minimise blood-air contact, we cannot guarantee the accuracy of all of the lower bicarbonate values. As patient weights and nPNA have stabilised we suspect that patients have adapted to the lower dialysate bicarbonate, whether this policy results in a lower incidence of calciphylaxis, or risks increased bone fracture rates will require a much longer follow-up. Ideally, dialysate bicarbonate should be individualised, but until such technology becomes generally available then clinicians have to decide on a one size fits all approach. As shown by our change in clinical practice opting for a lower bicarbonate dialysate reduces high post-HD values, but significantly increases low bicarbonate pre-HD values. Whether all such patients should then be prescribed oral bicarbonate to correct acidosis remains to be determined.

Declarations

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Code availability - Not applicable

Authors' contributions

SL collected data, tabulated and analysed data

And approved final version
AD conceived audit, wrote the 1st draft manuscript

Additional declarations - retrospective audit complied with UK National Research Ethics guidelines approval

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Figure 1. Consort flow diagram of patient numbers studied

Figure 2. Univariate correlation between pre-dialysis serum bicarbonate and change in serum bicarbonate with dialysis. For patients dialysing with a dialysate bicarbonate of 28 mmol/L, then $r = -0.62$, $p<0.001$; and for

those dialysing with a dialysate bicarbonate of 32 mmol/L, then r = 0.56, p<0.001.

Figure 3. Univariate correlation between dialysis to serum bicarbonate gradient and change in serum bicarbonate with dialysis. For patients dialysing with a dialysate bicarbonate of 28 mmol/L, then r = 0.62, p<0.001; and for those dialysing with a dialysate bicarbonate of 32 mmol/L, then r = 0.56, p<0.001.

Table 1. Dialysis session data and standard mid-week pre-dialysis laboratory results for patients dialysing with a bicarbonate of 32 and 28 mmol/L. Dialysate bicarbonate (bicarbonate), pre-dialysis serum bicarbonate mmol/L (PreBic) and post-dialysis (Post Bic), and change in serum bicarbonate (ΔBic), pre-dialysis weight (Weight), percentage weight loss with dialysis session (% Wt loss), sessional dialyser urea clearance (Kt/V), normalised nitrogen appearance rate g/kg/day (nPNA), dialysis session time minutes (Session time), haemoglobin (Hb), C reactive protein (CRP),serum calcium and phosphate both mmol/L, and creatinine umol/L, parathyroid hormone (PTH, creatinine index (CI), lean tissue index (LTI).).. Data expressed as integer, percentage, mean ±standard deviation,

or median and interquartile range. *, p<0.05, **<0.001, *** <0.001 vs dialysing with dialysate bicarbonate of 32 mmol/L

variable	Nov 2019	May 2020	July 2020	May 2021	Sept 2021
bicarbonate	32	28	28	28	28
patients	126	119	110	88	75
% male	57.9	60.2	59.6	53.4	54.7
Age years	63.7±16.3	63.7±16.5	62.7±16.5***	64.7±16.8***	65.9±16.4***
Pre Bic	21.1±2.3	19.8±2.2***	20.0±2.3***	20.5±2.1***	19.4±2.7***
Post Bic	24.9±2.1	22.5±2.0***	23.0±2.1***	23.9±2.8***	23.1±1.8***
Δ Bic mmol/L	4(2-5)	3(1-4)***	3(1.3-5)	4(2-5)	4(2-5)
Weight kg	74.6±20.7	71.7±18.2*	73.5±20.1	73.7±21.1	75.0±21.3
% Wt loss	2.3±1.2	2.3±1.4	1.5±0.8*	2.1±1.1	2.6±1.5
Kt/V	1.37±0.36	1.34±0.34	1.36±0.37	1.41±0.31	1.45±0.3*1
nPNA	0.82±0.18	0.77±0.2*	0.79±0.29	0.78±0.19	0.81±0.16
Session time	210(180-240)	210(180-240)	210(180-240)	210(180-240)	225(180-240)
Hb g/L	107±13	106±12	111±10*	108±13	108±13
Albumin g/L	39.7±4.2	37.7±4.9***	39.3±4.3	38.7±3.5*	37.6±4.0***
CRP mg/L	7(3-18)	8(3-17)	7.5(3-14)	6(2-15.3)	7(3-17)
Calcium	2.34±0.17	2.30±0.18	2.30±0.23	2.34±0,17	2.31±0.18
Phosphate	1.74±0.49	1.76±0.50	1.74±0.53	1.73±0.48	1.67±0.55
PTH pmol/L	32(17-54)	34(20-60)	354(21-54)	41(25-59)	40(20-57)
Creatinine	710(553-893)	674(527-883)*	738(556-967)	755(578-866)	742(589-924)
CI mg/kg/day	19.7±3.5	19.9±3.6	23.8±3.1***	19.1±3.0	19.0±1.3
LTI kg/m^2	17.8±4.5	17.3±4.5	20.4±5.3***	17.4±4.7	17.6±3.9

Table 2. Comparison of dialysis sessions of 180-, 210- and 240-minutes duration and using a dialysate bicarbonate of 32 of 28 mmol/L. Dialysate bicarbonate (dialysate), pre-dialysis serum bicarbonate mmol/L (Pre Bic) and post-dialysis (Post Bic), and change in serum bicarbonate (ΔBic), pre-dialysis weight (Weight), percentage weight loss with dialysis session (% Wt loss), sessional dialyser urea clearance (Kt/V), normalised nitrogen appearance rate g/kg/day (nPNA), dialysis session time minutes (Session time), β2 microglobulin (β2M), haemoglobin (Hb), C reactive protein (CRP),serum calcium and phosphate both mmol/L and creatinine umol/L. Data expressed as integer, percentage, mean ±standard deviation, or

median and interquartile range. *, p<0.05, **<0.001 , *** <0.001 vs dialysing with dialysate bicarbonate of 32 mmol/L

Session	180 minutes		210 minutes		240 minutes	
dialysate	Bic 32	Bic 28	Bic 32	Bic 28	Bic 32	Bic 28
sessions	23	188	50	110	31	115
Age years	66.3±11.8	65.8±15.1	65.7±17	63.7±15.9	61.6±14.1	62.4±15.3
Pre Bic	21.4±2.3	20.3±2,3*	21.2±2.3	19.2±2.5***	21.7±1.8	20.02.3***
Post Bic	24.6±2.0	23.5±1.9**	25.1±1.9	22.7±2.1***	25.4±2.0	23.3±2.0***
Δ Bic	3(1-5)	3(2-5)	4(2-6)	3(1-5)**	4(3-5)	4(2-5)
Pre Wt kg	65.8±19.5	69.8±18.2	67.4±18.8	71.9±21.1	78.2±20.8	77.5±19.3
% Δ Wt	1.4±0.7	1.5±0.7	1.8±0.8	1.7±0.1.2	2.2±0.8	2.0±0.8
Kt/V	1.33±0.35	1.30±0.32	1.42±0.34	1.35±0.32	1.48±0.32	1.39±0.35
nPNA	0.79±0.21	0.76±0.19	0.83±0.20	0.78±0.19	0.89±0.17	0.78±0.17
Hb g/L	105±15	108±14	107±12	107±12	109±12	108±12
Albumin g/L	39.5±4.3	37.7±4.6*	38.7±5.4	37.6±4,2	39.5±4.5	38.3±3.9
CRP mg/L	9(4-20)	6(2-14.5)	7(2-19)	8(3-15)	6(4-13)	7(3-15)
Calcium	2.39±0.19	2.33±0.17	2.35±0.17	2.29±0.20	2.31±0.18	2.30±0.17
Phosphate	1.66±0.4	1.83±0.58	1.79±0.62	1.72V0.54	1.67±0.42	1.72±0.53
Creatinine	616(512-817)	633(509-819)	716(505-957)	689(565-868)	742(560-925)-	776(596-982)

Table 3. Variables associated with change in serum bicarbonate on univariate analysis. Biochemical variables are pre-dialysis.

variable	r	p
Serum bicarbonate mmol/L	-0.58	<0.001
Normalised protein nitrogen accumulation g/kg/day	0.34	<0.001
Serum creatinine umol/L	0.26	<0.001
Serum albumin g/L	0.13	0.005
Age years	-0.09	0.042

Dialysis session time minutes	0.08	0.093

Table 4. Multivariable step-backward logistic model of variables independently associated with an increase in serum bicarbonate with dialysis. Standard error β (StE β), standardised coefficient (StandCoEff β). Pre-dialysis serum bicarbonate mmol/L (PreBic), normalised protein nitrogen accumulation g/kg/day (nPNA), dialysate bicarbonate 28 mmol/L vs 32 mmol/L (Dial 28), log dialysis session duration minutes (time). Model r^2 = 0.39

variable	β	StE β	StandCoEff β	T statistic	95% confidence intervals	p
PreBic	-0.51	0.05	-0.5	-11.3	-0.60 to -0.42	<0.001
nPNA	1.67	0.36	0.2	4.6	0.96 to 2.38	<0.001
Dial 28	-1.13	0.21	-0.23	-5.3	-1.54 to -0.74	<0.001
time	3.22	1.40	0.09	2.3	0.47 to 5.98	0.022