The choice of dialysate bicarbonate: do different concentrations make a difference?

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Metabolic acidosis is a common complication of chronic kidney disease; it is typically caused by the accumulation of sulfate, phosphorus, and organic anions. Metabolic acidosis is correlated with several adverse outcomes, such as morbidity, hospitalization, and mortality. Thus, correction of metabolic acidosis is fundamental for the adequate management of many systemic complications of chronic kidney disease. In patients undergoing hemodialysis, acid-base homeostasis depends on many factors including the following: net acid production, amount of alkali given by the dialysate bath, duration of the interdialytic period, and residual diuresis, if any. Recent literature data suggest that the development of metabolic alkalosis after dialysis may contribute to adverse clinical outcomes. Our review is focused on the potential effects of different dialysate bicarbonate concentrations on hard outcomes such as mortality. Unfortunately, no randomized studies exist about this issue. Acid-base equilibrium is a complex and vital system whose regulation is impaired in chronic kidney disease. We await further studies to assess the extent to which acid-base status is a major determinant of overall survival in patients undergoing hemodialysis. For the present, the clinician should understand that target values for predialysis serum bicarbonate concentration have been established primarily based on observational studies and expert opinion. Based on this, we should keep the predialysis serum bicarbonate level at least at 22 mmol/l. Furthermore, a specific focus should be addressed by the attending nephrologist to the clinical and nutritional status of the major outliers on both the acid and alkaline sides of the curve.

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Metabolic acidosis is present in the majority of patients with chronic kidney disease (CKD) when the glomerular filtration rate decreases to less than 20% to 25% of normal, although as many as 20% of individuals can have acid-base parameters close to or within the normal range. Acidosis generally is mild to moderate in degree, with plasma bicarbonate (BIC) concentrations ranging from 12 to 22 mmol/l, and it is rare to see values less than 12 mmol/l in the absence of an increased acid load. The degree of acidosis approximately correlates with the severity of renal failure and usually is more severe at a lower glomerular filtration rate. The metabolic acidosis can be of the high anion gap variety, although the anion gap can be normal or only moderately increased even with stage 4 to 5 CKD. Several adverse consequences have been associated with metabolic acidosis, including muscle wasting, bone disease, impaired growth, abnormalities in growth hormone and thyroid hormone secretion, impaired insulin sensitivity, progression of renal failure, and exacerbation of β_2-microglobulin accumulation.[1] Metabolic acidosis results from the imbalance between the whole-body net production of acid and acid removal by the kidney.[2] Endogenous acid production depends primarily on diet. It has the most important effect in the development of acidosis: animal proteins contain greater amounts of sulfate and phosphorus than do vegetable proteins, which conversely increase alkali production. Metabolic acidosis in severe CKD is typically caused by the accumulation of sulfate, phosphorus, and organic anions; thus, normochloremic acidosis with a high anion gap is a common picture in advanced CKD.[1]

Acid-base balance in patients undergoing hemodialysis

Hemodialysis (HD) has historically used acetate buffer in dialysate. High concentrations, up to 40 mmol/l, result in BIC generation after liver metabolization. Nonetheless, at such concentrations, acetate is a potent vasodilator and myocardial depressor and can cause intradialytic hypotension. Acetate has been replaced over time by BIC. Many centers use BIC concentrations in the dialysate (D_{BIC}) on the order of 32 to 39 mmol/l. Such levels are often obtained with a 3-stream method using a proportioning dual-concentrate system that mixes water with a "base concentrate" containing liquid or powder sodium and an "acid concentrate" in either a liquid or solid form and containing sodium chloride, calcium chloride, magnesium chloride, potassium chloride, glucose monohydrate, and an organic acid. The latter is necessary because the mix of BIC and calcium requires a small amount of acid

to avoid insoluble precipitation of calcium carbonate. The organic acid can be in the form of glacial acetic acid, sodium diacetate, lactic acid, or citric acid.[3] Sodium diacetate is composed of approximately 50% acetic acid and 50% sodium acetate. Should one choose to use sodium diacetate as the organic acid and to aim for the presence of 4 mmol/l of acetic acid in the final dialysate, one needs to provide 4 mmol/l of sodium diacetate (containing 4 mmol/l of acetic acid and 4 mmol/l of sodium acetate) to the final dialysate by way of the acid concentrate. The acetate in the sodium acetate will increase the total amount of buffer base (the sum of BIC and BIC precursors [acetate in this case]) in the final dialysate. When using sodium diacetate, the additional source of buffer base should be kept in mind.[3] It should also be kept in mind that a potential risk of hypervolemia and hypertension may exist because of the increased total amount of sodium in the final dialysate. Even these small amounts of acetate in the dialysate have been shown to cause hemodynamic instability.[4] Finally, a recent registry-based study has shown an improved survival associated with acetate-free HD in patients aged 70 years and older.[5] Sodium BIC is the main buffer used during maintenance HD, and patients who undergo this procedure receive high doses of sodium BIC for their life span.

New BICs are primarily added directly from the bath, although a small amount is also generated from the addition and metabolism of acetate, citrate, or acetic acid (or a combination) (Figure 1). With D_{BIC} set at 35 mmol/l, average predialysis serum BIC at the beginning of the week ranges from 20 to 24 mmol/l; individual values, however, range from less than 17 mmol/l to more than 27 mmol/l.[6] Serum BICs normally increase rapidly during the first 2 hours of treatment and then level off, ending the treatment at a level about 4 to 7 mmol less than D_{BIC}.[7] The reason postdialysis serum BIC does not approach D_{BIC} likely results from stimulation of organic acid production by the added BIC, an event that consumes this alkali and minimizes further increases in serum BIC. The amount of organic acid produced is difficult to quantitate and may vary considerably from patient to patient.[6] In patients undergoing HD, acid-base homeostasis depends on many factors: net acid production, amount of alkali given by the dialysate bath, duration of the interdialytic period, as well as residual diuresis, if any. The mass of BIC added during dialysis is a function of its dialysance and the integral over the time of treatment of its transmembrane concentration gradient[8]:

$$BICs\ added\ =\ dialysance \times \int_{o}^{t} (D_{BIC} - blood\ [BIC])$$

where dialysance is a measure of the rate of movement of BIC across the dialysis membrane, expressed in ml/min, and is dependent on the surface area and permeability of the membrane used as well as on blood and dialysate flow rates[8] (Figure 1). When measured at a blood flow rate of 200 ml/min and a dialysate flow rate of 400 ml/min using a regenerated cellulose membrane with a surface area of 1.8 m^2, dialysance is 131 ml/min or about 65% of blood flow rate.[9] When comparing bicarbonate kinetics and acid-base status in high-flux HD and on-line postdilution hemodiafiltration (D_{BIC} was 38 mmol/l in both treatments; the mean reinjected volume was 21 L in hemodiafiltration), no significant differences were observed between acid-base parameters at the end of HD and hemodiafiltration sessions. An unexpected result was the continuous decay of BIC dialysance both in HD and hemodiafiltration runs.[10] These data confirm the *in vitro* data obtained by the same group.[11] Thus, BIC dialysance behaves very differently from urea clearance, even though both solutes have a similar molecular weight.[10,11] Because predialysis serum BICs are a function of endogenous acid production in the interdialysis period, alkali addition is by definition equal to endogenous acid production. Because the membrane characteristics, dialysis duration, and bath solution are all
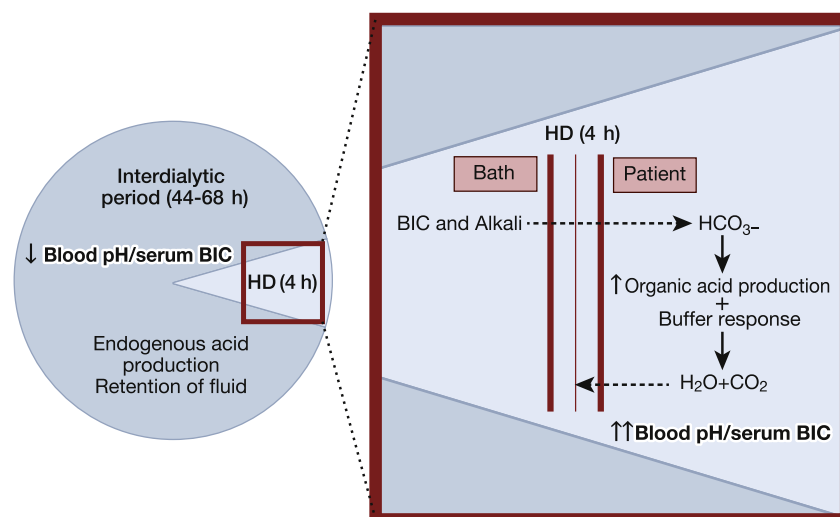

Figure 1 | The events governing blood pH and serum bicarbonate (BIC) changes occurring during an entire cycle (intra- and interdialysis periods). No ultrafiltration occurs in this simplified model. HD, hemodialysis.