Dual-concentrate bicarbonate-based hemodialysis: know your buffers

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Dual-concentrate bicarbonate-based dialysate delivery systems offer many advantages including individualized dialysate prescription. Many concentrates are available commercially containing different mixtures of acetic acid, citric acid, sodium acetate and sodium bicarbonate. Nephrologists must be familiar with the total equivalents of buffer base available for administration via the final dialysate to the patient at a specific machine setting and concentrate pairing in order to achieve optimal acid-base balance and avoid under-correction or overcorrection of acidosis and their associated deleterious effects.

Recently the U.S. Food and Drug Administration (FDA) sent an alert to health care providers to consider the presence and quantity of acetate, citrate, and/or acetic acid in dialysate concentrates when determining the patients' dialysate prescription amidst concerns regarding metabolic alkalosis[1]. This culminated in a recall of a sodium diacetate-containing concentrate due to potential serious adverse consequences including death.

Dialysate buffer content is designed to correct the metabolic acidosis that regularly occurs with renal failure. The catabolism of proteins produces non-volatile acids, such as phosphoric and sulfuric acids. Approximately 0.77 mEq of hydrogen is generated per gram of protein catabolized [2]. This acid load is neutralized by body bicarbonate which needs to be replenished in dialysis patients by the provision of buffers during dialysis. These buffers can be in the form of bicarbonate and/or bicarbonate precursors such as acetate, lactate or citrate. Bicarbonate dialysate is usually produced by mixing water with an 'acid concentrate' and a 'base (i.e. bicarbonate) concentrate'. This methodology applies to both the batch and proportioning systems. In a batch system the dialysate is mixed in a tank that is sealed to prevent the loss of carbon dioxide generated by the reaction between the acid and bicarbonate components [3]. In a

proportioning system the dialysis machine proportions the acid concentrate, the base concentrate and purified warm water in situ, without the need for a dialysate storage tank.

The base concentrate

The base concentrate contains powdered or liquid sodium bicarbonate (some base concentrates also contain sodium chloride). For example, one conventional base concentrate on the market contains 81.25 grams of sodium bicarbonate per liter (or 967 mmol/L as the molecular weight of sodium bicarbonate is 84). Since it is made for hemodialysis equipment for a 1: 1.72: 42.28 proportioning (acid concentrate: base concentrate: water; also known as 45X preparation) one can calculate the bicarbonate concentration in the final dialysate (before reaction with acid, please see below) to be 37 mEq/L. Because of the high risk of bacterial contamination of liquid bicarbonate solutions, a cartridge of dry sodium bicarbonate was developed (BiCart®, Gambro Lundia AB, Lund, Sweden[4]). Water is drawn by the dialysis machine through the cartridge, producing a saturated solution of sodium bicarbonate (1,000 mmol/L).

The acid concentrate

A conventional acid concentrate typically contains the chloride salts of sodium, calcium, magnesium and potassium, glucose monohydrate, and an organic acid. The organic acid used in the 'acid concentrate' can be in the form of glacial acetic acid, lactic acid ([5]), or citric acid ([6]). The acid concentrate may also contain the salt of an organic acid, such as sodium acetate. The purpose of the acid is to lower the pH of the dialysate to below 7.3 so that calcium and magnesium do not precipitate out of solution in the form of carbonate salts when bicarbonate is added. It is important to realize, when calculating the total buffer base in the final solution, that

the added organic acid (a proton donor) will consume an equivalent amount of bicarbonate in the final dialysate solution. As an example, if glacial acetic acid (MW 60) is used the following reaction will take place with bicarbonate (henceforth referred to as the reaction):

$$NaHCO_3 + CH_3COOH \rightarrow H_2CO_3 + CH_3COONa \rightarrow CO_2 + H_2O + CH_3COONa$$

Na bicarbonate + Acetic acid $\rightarrow$ Carbonic acid + Na acetate $\rightarrow$ carbon dioxide + water + Na acetate

If the bicarbonate concentration (and the buffer base level) in the dialysate, before the reaction with the acetic acid, were 37 mEq /L, and 4 mmol/L of acetic acid were added, then in the final dialysate there would be only 33 mEq /L of bicarbonate remaining along with 4 mEq/L of acetate (as sodium acetate). In other words, in the final dialysate, the loss of bicarbonate is balanced by a gain in acetate. Some, if not all, of this acetate will gain access into the blood stream as a result of dialysis; the acetate will normally be metabolized to generate bicarbonate via the Krebs citric acid cycle. The addition of acetic acid consumes an equimolar amount of bicarbonate but the total buffer base available to the patient (the sum of bicarbonate and acetate) in the final dialysate does not change; it remains at 37 mEq/L (33 from bicarbonate and 4 from acetate). This is so because acetate is a bicarbonate precursor.

GranuFlo® (Fresenius Medical Care, Waltham, MA, USA) is a dry acid concentrate product that was introduced to the market over a decade ago. It contains dry sodium diacetate, a compound with a formula of $NaH(C_2H_3O_2)_2$ [MW 142]. Sodium diacetate eliminates the need for handling the hazardous liquid glacial acetic acid. Additional marked advantages of powdered concentrates over liquid concentrates are the substantially reduced weight and smaller required storage space. These advantages would also hold true for bicarbonate powder and dry forms of lactic acid or citric acid. The reduced weight is an important factor in cutting shipping costs. Sodium diacetate

is made up of equal parts of acetic acid and sodium acetate. The product dialysate contains a total of 8 mEq/L of acetate, 4 originating from acetic acid and 4 from sodium acetate. The 4 mmol/L of acetic acid in this preparation will behave in a manner similar to that described above for glacial acetic acid. It is the additional 4 mmol/L of sodium acetate provided by this product that will increase the total buffer base load and may foster metabolic alkalosis. If the original pre-reaction bicarbonate level (before reaction with acetic acid) is 37 mEq/L, the total buffer base (bicarbonate and acetate) in the final dialysate will be 41 mEq/L. Of the 41 mEq/L, 33 are from the remaining bicarbonate after reaction with acetic acid and 8 are from acetate. If a total buffer base value of 41 mEq/L is deemed too high for an individual patient's needs, then the bicarbonate level should be lowered on the dialysate screen setting (see proportioning system below). A better approach could be for the manufacturer to produce an appropriate base concentrate containing less bicarbonate (and more chloride).

Citric acid can also be used in the place of acetic acid in the acid concentrate and is available in both powder and liquid forms. The formula for citric acid is $C_6H_8O_7$ (MW 192) and the acid has three -COOH groups. One mmole of citric acid has 3 mEq of hydrogen and 3 mEq of citrate. Ahmad et al. (6) prepared an acid concentrate from dry chemicals including citric acid, conventionally used electrolytes and dextrose and a small amount of sodium acetate (DRYalysate, Advanced Renal Technologies, Kirkland, WA). These chemicals were mixed with treated water to yield an acid concentrate. The concentration of citric acid in the dialysate (before reaction with bicarbonate) was 0.8 mmol/L (2.4 mEq/L of citrate) and that of sodium acetate was 0.3 mmol/L. The bicarbonate concentrate provided 37 mEq/L of bicarbonate (pre-reaction). The reaction between citric acid and bicarbonate is similar to the case of acetic acid described above. Citrate (like acetate) will be metabolized by the citric acid cycle to form

bicarbonate. The small amount of sodium acetate (0.3 mmol/L) will also yield bicarbonate bringing the total buffer base to 37.3 mEq/L (34.6 mEq/L post-reaction remaining bicarbonate, plus 2.4 mEq/L from citrate plus 0.3 mEq/L from acetate). In a 12-week study during which a citric acid-containing acid concentrate was used exclusively, pre-dialysis mean serum bicarbonate concentration rose, with normalization of the originally low serum bicarbonate level in the majority of the patients. Moreover improved clearance of various solutes was also noted with the use of a citrate-containing dialysate (6,[7]).

The proportioning system

As noted above, many current hemodialysis machines have a proportioning system for on-line dialysate preparation. Proportioning systems were first introduced in the early 1960's ([8],[9]). Since a modern 3-stream proportioning system uses 2 concentrates, such an approach permits some variation in the final dialysate bicarbonate concentration by altering the delivery rate of the bicarbonate concentrate relative to the acid concentrate ([10], [11],[12]). One has to refer to the operator manual of the individual dialysis machine to obtain the final dialysate options based on a compatible concentrate-pair and standard proportioning ratio. For example, in the Phoenix® dialysis machine (Gambro Lundia AB), one can set the bicarbonate conductivity (in milliSiemens/cm) at a certain value to achieve a desired dialysate bicarbonate level (using certain concentrates) and also set a final dialysate conductivity which correlates with the desired sodium concentration in the final dialysate. Several dialysis machines allow for choosing the bicarbonate concentration in the final dialysate with an adjustment range of 20-40 mEq/L.

When a lower bicarbonate concentration is desired, the rate of the bicarbonate concentrate addition to the final dialysate is reduced, and the rate of addition of the acid concentrate will be

reciprocally increased in order to maintain the dialysate sodium concentration in the prescribed range. This adjustment cannot be carried out by simply increasing the acid concentrate by a 1:1 volume ratio relative to the reduction in the bicarbonate concentrate as the sodium concentration in the acid concentrate is typically 3.5-4.5 times that in the bicarbonate concentrate. The exact algorithm used by the dialysis machine to determine the amount of acid concentrate needed is not detailed in the various dialysis machine operator manuals. Clearly, as potassium, calcium and magnesium are also contained in the acid concentrate, altering the relative delivery rate of the acid concentrate will result in changes in the final concentrations of potassium, calcium and magnesium as well.

Serum bicarbonate level

During bicarbonate dialysis the bicarbonate dose (or total buffer base dose) that is delivered to the patient is dependent on the concentration gradient for bicarbonate between the dialysate and the plasma water and the efficiency of the dialysis. The change in serum bicarbonate (post-dialysis *vs.* pre-dialysis level) will also depend on the bicarbonate distribution space (estimated at 40-50% of total body weight). Pre-dialysis bicarbonate level will be influenced by factors such as protein intake (due to acid generation in the interdialytic period), use of parenteral nutrition, use of phosphate binders (e.g., calcium carbonate, sevelamer chloride vs. sevelamer carbonate) and other bicarbonate-containing or bicarbonate-forming preparations, as well as gastric acid loss (e.g., from vomiting).

Dialysis machine manufacturers are encouraged to make the details of dialysate preparation by their machines readily available to health care providers. To that end it would be helpful to have all operator manuals available online. If bicarbonate level in the dialysate is displayed, it should

be clearly identified whether the value is pre- or post-reaction with the acid from the acid concentrate. If the bicarbonate level in the final dialysate is displayed as post-reaction with the acid, then the total organic anions that are bicarbonate precursors (e.g., acetate and citrate) present in the final dialysate must be added to arrive at the amount of the total buffer base dose. If the bicarbonate level is displayed as pre-reaction with the acid then only the portion of the organic anion (e.g., acetate) that originated from a salt of the same anion (e.g., sodium acetate) in the acid concentrate needs to be added to obtain the total buffer base dose.

Nephrologists need to assess their patients' pre-dialysis serum bicarbonate values on a regular basis and adjust their required dialysate total buffer base content accordingly.

Disclosure: Dr. Ing is a member of the Medical Advisory Board of Renal Solutions, Inc., a subsidiary of Fresenius Medical Care. The present article represents only the personal views of the authors.

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