
Core Curriculum

Composition and clinical use of hemodialysates

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Abstract

A thorough knowledge and understanding of the principles underlying the preparation and the clinical application of hemodialysates can help us provide exemplary patient care to individuals having end-stage renal disease. It is prudent to be conversant with the following: (a) how each ingredient in a dialysate works, (b) the clinical circumstances under which the concentration of an ingredient can be altered, and (c) the special situations in which unconventional ingredients can be introduced into a dialysate. The potential to enrich dialysates with appropriate ingredients (such as iron compounds) is limited only by the boundaries of our imagination.

Key words: Composition, use, dialysates

INTRODUCTION

Dialysate composition and preparation along with dialysate use is probably one of the most fascinating topics in nephrology, where the possibilities for innovative tinkering and improvements are plentiful. Furthermore, learning about the art and the science of fashioning dialysates is one of the best ways to further the understanding of the patho-physiologic processes underlying myriad acid-base, fluid, electrolyte, as well as blood pressure abnormalities. On the other hand, a thorough knowledge of the above patho-physiologic processes will immensely enhance the understanding of the basic principles under which dialysates are produced.

Not only can the concentrations of different normally present constituents be varied but also many unconventional compounds can be used to enrich a dialysate. In recent years, many reports have surfaced on the addition of urea, phosphorus, ethanol, citric acid, and even iron to

a dialysate.^{1–5} This enrichment approach may represent the harbinger of a “designer dialysate” era, as the opportunities for modifying dialysate composition are considerable in a variety of situations not uncommonly encountered in clinical medicine. Herein, we review the composition of a conventional dialysate, the reason for the presence of the various constituents, and possible modifications that one can make with regard to both regular and unfamiliar ingredients.

SODIUM (MW 23)

Of all the electrolytes in the human plasma, sodium is the most abundant (normal plasma sodium is 138 mmol/L and is accompanied by a corresponding number of anions). Consequently, plasma osmolality level (normal being 287 mmol/kg) is closely tied to the plasma sodium value. It should be noted that the dialysate sodium level determines not only (a) the sodium exchanges between the dialysate and the plasma, and secondarily those between the plasma and the extracellular fluid (ECF) but also (b) the water exchanges between the dialysate and

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the plasma, those between the plasma and the ECF, and those between the ECF and its intracellular counterpart.

In the early days of hemodialysis, as the coil dialyzers in use at the time could not withstand high transmembrane hydrostatic pressures well, water removal during dialysis was accomplished using large amounts of glucose (e.g., more than 1,800 mg/dL) in the dialysate, taking advantage of a process known as osmotic ultrafiltration.⁶ Because the concentration of water in the plasma was then higher than that in the dialysate (or, in other words, the osmolality was higher in the dialysate than in the plasma), water would flow from the plasma into the dialysate. Therefore, if an isonatric dialysate were to be used, hyponatremia would invariably result. Consequently, during those early days, dialysate sodium concentrations were purposely kept low, e.g., in the order of 126 to 130 mmol/L.⁶ Subsequently, however, more resilient membranes that could withstand higher transmembrane pressures were developed. These new membranes were incorporated into plate and capillary dialyzers with enclosed dialysate compartments, making it possible to remove fluid by changing the transmembrane pressure.⁷ This latter process is known as hydrostatic ultrafiltration. With this new technique, the need to raise dialysate glucose concentration was no longer present. The approach of lowering the dialysate glucose concentration coincided with that of elevating the dialysate sodium level (e.g., to between 130 and 137 mmol/L).⁶

Apart from the removal of waste products, an important goal of dialysis is to dispose of sodium and water gains obtained during the preceding interdialytic interval without making significant changes in the plasma sodium concentration. An ultrafiltration volume that matches the amount of sodium and water accumulated during the interdialytic period is thus required (assuming that the patient has already achieved a “dry weight” status). In addition to proper ultrafiltration, in order to meet the above goal, dialysates with appropriate sodium concentrations should be used. With hydrostatic ultrafiltration, sodium is removed at a rate closely similar to water, thus allowing the plasma sodium level to remain relatively constant. It should be noted that the majority of sodium and water is removed by ultrafiltration than by diffusion. For example, every liter of ultrafiltrate will remove an amount of sodium that closely approximates the amount present in a liter of the corresponding plasma. If one obtains 2 L of ultrafiltrate in a dialysis session, approximately 270 mmol of sodium will be removed.

There are a myriad of factors for consideration in determining what the sodium level of a dialysate should be. These factors include the sodium ion activity in plasma

(some sodium in plasma is bound to anions), the Gibbs–Donnan phenomenon, and the entry of water from the ECF into cells as dialysis proceeds. First, as some of the plasma sodium is bound to anions, not all the plasma sodium is freely diffusible. Indeed, a gradient of sodium activity of at least 4 mmol/L between plasma and dialysate needs to exist before any diffusive losses can result.⁸ Secondly, as albumin is negatively charged and does not cross the semi-permeable dialyzer membrane to reach the albumin-free dialysate, it produces an attractive force for cations such as sodium to remain in the plasma, thus promoting the tendency to have a higher plasma sodium level relative to that of dialysate (the Gibbs–Donnan phenomenon).⁹ Thirdly, during dialysis, plasma and interstitial fluid osmolalities fall because of the removal of urea, potassium, and other osmotically active waste products. The lowering of plasma and interstitial fluid osmolalities will drive water into cells, while sodium will remain behind in the extracellular space. The loss of water without a corresponding concomitant loss of sodium from the ECF will cause the latter's sodium concentration to rise. In this regard, Moret et al.¹⁰ observed that a dialysate sodium concentration of 140 mmol/L would not bring about any changes in the plasma sodium value postdialysis, whereas a dialysate sodium concentration of 144 mmol/L would lead to higher plasma sodium concentrations postdialysis when compared with predialysis. With so many patho-physiologic factors such as those described above affecting the behavior of sodium in both the plasma and the dialysate, figuring out the best dialysate sodium level for a particular patient is not an easy task. Suffice it to say that dialysates with sodium levels between 135 and 145 mmol/L have fulfilled their expectations and are most often used.¹¹

With the advent and almost universal adoption of short dialysis (thrice weekly regimen with 4 hr or so of treatment time for each session) in the early 1970s, the control of ECF volume and blood pressure became more difficult.¹² The occurrence of hypotension during such dialysis is not uncommon. The hypotension episodes are caused by hypovolemia induced by excessive ultrafiltration (i.e., too much ultrafiltration in too short a time) that has outstripped the counter-measuring vascular refilling rate. In many units, one solution has been to elevate the sodium concentration in the dialysate¹² from, for example, 135 mmol/L (often used in the 1970s) to 145 mmol/L or higher in an attempt to raise the plasma sodium value. A high plasma sodium level will not only help retain water within the vascular space but will also attract water from the interstitial and intracellular compartments to ensure the maintenance of a more adequate plasma vol-

ume and, hence, higher blood pressure.¹³ However, at the same time, the intradialytic fall in plasma urea and osmolality levels tends to direct water to move in the opposite direction.¹⁴ In terms of increasing dialysate sodium concentration, an array of different approaches have been suggested, including ones with a continuously high sodium concentration and ones that start out with a high sodium value (e.g., 145–150 mmol/L), which subsequently falls in a linear, step, or logarithmic manner to a lower level (e.g., 135–140 mmol/L) as dialysis progresses (sodium profiling).¹⁵ Noteworthy that a patient's post-dialysis plasma sodium value is a function of a treatment's time-averaged dialysate sodium value, not the terminal dialysate sodium concentration.¹⁶ The effect of raising dialysate sodium value in any fashion has been analyzed in many studies. Almost all of them arrived at a similar conclusion, namely, increasing dialysate sodium concentration reduces intradialytic morbidity and the early post-dialysis fatigue, but augments thirst, interdialytic weight gain, and ultimately, the prevalence of high blood pressure.¹² In spite of the above-described drawbacks, hypernatric dialysates may still have a role to play in the management of those patients who suffer from inordinately profound intradialytic hypotension [although another approach for such patients centers on more frequent (e.g., short daily dialysis),¹⁷ or more prolonged but more gentle (e.g., long, daily nocturnal dialysis,¹⁸ with smaller blood and dialysate flow rates as well as slower ultrafiltration rate) dialysis regimens]. For those intradialytic hypotension-prone patients who can be helped by the use of high-sodium dialysates but do not develop fluid overload and hypertension despite such use (which means these patients can lose sufficient amounts of sodium and water via their residual renal function), the use of such high-sodium dialysates would appear to be reasonable. In addition, dialysis patients with inordinately high plasma urea concentrations may also benefit from the use of hypernatric dialysates.¹⁹ However, the advantage of this latter approach still awaits confirmation.

In hypernatremic patients who require dialysis, a safe approach is to carry out dialysis using dialysate sodium levels that are close (within 2 mmol/L) to the sodium values in the plasma. Subsequently, the hypernatremia can be corrected by the slow administration of isotonic saline or of slightly hyponatric fluids. In this way, hypotension (occurring on account of contraction of the plasma volume subsequent to the loss of water to the relatively hyperosmolar interstitium) and cerebral edema, both taking place as a result of the abrupt lowering of plasma sodium level can be minimized or avoided.²⁰ In the case of patients with long-standing, moderate-to-severe hypo-

natremia (plasma sodium level below 125 mmol/L) who require dialysis, the ideal management approach is not known. For these patients, at this stage of incomplete knowledge, it has been suggested that it would seem prudent to set the dialysate sodium level no higher than 15 to 20 mmol/L above the plasma value with the intent of rectifying the hyponatremia only after multiple dialysis treatments performed over several days.²⁰ It has also been suggested that the correction rate for severe chronic hyponatremia should be no higher than 12 mmol/L over 24 hr.²¹ Again, whether this recommendation applies to dialysis patients is also unknown. The above precautionary measures are necessary because correcting hyponatremia too rapidly has been found to precipitate the osmotic demyelination syndrome in a variety of patients.²² It cannot be overemphasized that in the treatments of both hypernatremia and hyponatremia, the general standard practice guidelines recommended for such treatments should be followed. In addition, frequent monitoring of plasma sodium values during treatment is mandatory.

POTASSIUM (MW 39)

Under normal circumstances, potassium removal during dialysis should be equal to the amount accumulated during the interdialytic period. The magnitude of plasma potassium concentration is dependent upon dietary potassium intake, dialysate potassium concentration, the efficiency (KoA) of the dialyzer, the duration and frequency of dialysis as well as fecal excretion.^{23,24} For these reasons, there is no single ideal value for dialysate potassium level that is applicable to all clinical situations. Furthermore, the plasma potassium concentration is not a reliable index of total body potassium content, although persistently low predialysis plasma levels of potassium are suggestive of a total body deficit. The rate of potassium removal during dialysis is largely a function of the predialysis concentration.²⁵ The higher the initial plasma concentration, the greater the gradient between the plasma and the dialysate and, hence, the greater the potassium removal. Likewise as the plasma potassium concentration falls, the removal becomes less efficient.

The Nernst equation indicates that the electrical activity of the heart is related to the ratio between the intracellular and extracellular potassium ion levels.²⁶ With the use of a low-potassium dialysate, one removes potassium mainly from the extracellular space and very little from the intracellular one. Surprisingly, most dialysis patients are able to tolerate the intradialytic increase in hyperpolarization of the cardiac muscle membrane potential,

induced by a rise in the intracellular potassium level/extracellular potassium level ratio brought about by a reduction in the extracellular potassium value as a result of dialysis. However, it is not infrequent to encounter a patient with heart disease who develops arrhythmias during dialysis. Using a higher potassium dialysate is necessary for these patients.

The dietary intake of potassium approximates 60 to 80 mmol/day. Although the most efficient way to remove potassium would be 2–3 hr of dialysis interrupted by several hours of no dialysis,²⁷ such an approach is not practical because of the inherent inconvenience. In the case of a conventional, thrice-weekly (4 or less hours per session) dialysis regimen, by using modern dialysis equipment as well as proper blood and dialysate flow rates, control of body potassium can readily be achieved by adjusting dialysate potassium values (e.g., commonly using 0–2 mmol/L) in the majority of patients. In this regard, the colon contributes considerably to potassium removal in dialysis patients, with colonic disposal being about 30% of the dietary intake, a value that is about 3 times normal.^{24,28} Finally, under conditions in which dietary potassium intake is reduced temporarily, e.g., as a result of an intercurrent illness, the use of a higher potassium bath might be necessary.

Unlike the extracellular potassium, which can freely pass across the dialysis membrane, the intracellular potassium is slow to move into the extracellular space. This latter movement is influenced by a variety of factors, which can change during a dialysis procedure.^{29,30} Alkalosis causes a shift of potassium into cells and acidosis results in a potassium efflux from cells. Introduction of buffer base into blood during dialysis promotes cellular uptake of potassium and thereby attenuates the dialytic removal of potassium (this is more evident in an acidotic patient). However, with routine dialysis, the change in blood pH is small and does not affect potassium removal appreciably. There are case reports describing that dialysis succeeded in reducing plasma potassium concentrations even though the dialysate potassium levels were higher than the original, predialysis plasma potassium values. The decline in plasma potassium concentration was associated with a corresponding, dialysis-induced rise in blood pH.³⁰

Insulin affects potassium removal during dialysis because it stimulates the cellular uptake of potassium. Studies comparing potassium removal using glucose-free and glucose-enriched dialysates showed greater potassium removal with the use of the former dialysates.³¹ This is because glucose-free dialysates do not foster insulin secretion, thus allowing more potassium to be available

for removal by dialysis. Plasma tonicity also influences the distribution of potassium between the intracellular and extracellular spaces.⁶ It is suggested that increased tonicity induced by the use of hypertonic saline or mannitol in the treatment of hypotension occurring during dialysis would favor potassium efflux into the extracellular space. Similarly, β -adrenergic agents promote the movement of potassium into cells from the extracellular space. Allon et al.³² found a lower cumulative potassium removal in patients treated with nebulized albuterol 30 min prior to dialysis as compared with patients in whom albuterol treatment was not administered.

Hyperkalemia is still a major cause of death in patients treated by regular dialysis.³³ In the early days of hemodialysis, hyperkalemia was most readily corrected by withholding potassium from the dialysis fluid for the first 30–60 min of dialysis; extra caution was necessary in patients receiving digitalis or similar drugs.⁶ Use of low-potassium dialysates has been associated with the development of ventricular ectopic activity which is more pronounced in patients with left ventricular hypertrophy and/or those who are receiving chronic digitalis therapy.³⁴ The rate of decline in plasma potassium value directly correlates with the development of arrhythmias. Because of the above reason, for patients who are receiving digitalis therapy, dialysate potassium level is frequently set at a value higher than usual, e.g., at 2–3.5 mmol/L. Not surprisingly, it has been noted that the frequency of arrhythmias is greater during the first 2 hr of dialysis (because the rate of fall in plasma potassium level is greater due to the presence of a higher potassium concentration gradient).³⁵ When studying the effect of potassium removal on the QTC interval dispersion during dialysis, Cupisti et al.³⁶ observed a direct correlation between dialysis-induced hypokalemia and the QT dispersion. Potassium modeling first suggested by Redaelli et al. involves decreasing the potassium level in the dialysate exponentially to maintain a constant plasma to dialysate potassium gradient of 1.5 mmol/L so that the extracellular potassium level will not fall too abruptly to create a high intracellular potassium level/extracellular potassium level ratio (vs. a higher intracellular potassium level/extracellular potassium level ratio if a hyperkalemic patient were to be dialyzed with a potassium-free bath) in an attempt to minimize cardiac irritability and the occurrence of ventricular ectopic activity in high-risk individuals. The approach succeeded in reducing dialysis-induced premature ventricular contractions, the effect being more prominent during the first hour of dialysis.³⁷ While the confirmation of these results of Redaelli et al. is awaited, it would seem prudent, in compliance with the notion

conveyed by the Nernst equation, to avoid lowering inordinately high plasma potassium levels too abruptly by dialysis. At this stage of incomplete knowledge, one possible approach might be starting with a higher dialysate potassium level and then reducing this initial level in a simple stepwise fashion as dialysis proceeds. However, it must be emphasized that there is still no consensus as to what is the best approach to dialyze a patient with marked hyperkalemia. In any case, one should be vigilant about the possibility of an early postdialytic plasma potassium rebound when intracellular potassium gains entry into the ECF because of the induction, by dialysis, of a higher concentration gradient between the intracellular and ECF potassium levels. Repetition of dialysis sessions or the administration of potassium-removing sodium polystyrene sulfonate may be necessary.

Not infrequently, dialysis patients who are fasting prior to surgery develop hyperkalemia, the occurrence of which is thought to be secondary to the lack of insulin.³⁸ In this situation, an additional dialysis session or lowering of the potassium level in the bath may be necessary.

BICARBONATE (MW 61)

One of the goals of hemodialysis is to correct metabolic acidosis associated with renal failure.³⁹ The acid production by the body mainly results from protein catabolism and is in the order of approximately 0.77 mmol/g of protein catabolized.⁴⁰ The adjusted survival of hemodialysis patients is reduced when predialysis bicarbonate concentration is less than 18 mmol/L or greater than 24 mmol/L.⁴¹ K-DOQI guidelines recommend a midweek predial-

ysis plasma bicarbonate level of 22 mmol/L.⁴² Dialysis rectifies metabolic acidosis mainly through buffer (bicarbonate or its precursors) supply rather than the removal of acid.

Many centers use dialysate bicarbonate concentrations in the order of 32–39 mmol/L. Such levels are often obtained by using a 3-stream method utilizing a proportioning, dual-concentrate system (Figure 1) that mixes water with a “base concentrate” containing powder or liquid sodium bicarbonate (along with sodium chloride in some preparations), and an “acid concentrate,” in either a liquid or a solid form and containing sodium chloride, calcium chloride, magnesium chloride, potassium chloride (if necessary), glucose monohydrate, and an organic acid. The commonly used proportioning ratios of concentrates and water include: 1:1.225:32.775, 1:1.83:34, and 1:1.72:42.28 (i.e., “acid concentrate”: “base concentrate”: water). The organic acid used in the “acid concentrate” can be in the form of glacial acetic acid, sodium diacetate,⁴³ lactic acid,⁴⁴ or citric acid.⁴ The amounts of such acids used (usually 2.4–5 mmol/L) in the case of monobasic acids in the final dialysate are geared to provide 2.4–5 mEq of hydrogen and the same number of mEq of the conjugate, organic anions. Sodium diacetate is composed of approximately 50% acetic acid and 50% sodium acetate and works in the following manner. 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

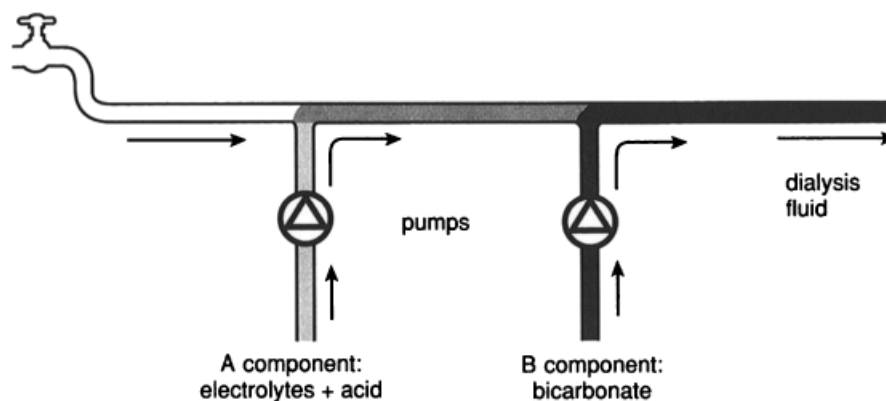


Figure 1 Three-stream method of preparing a bicarbonate-based hemodialysate using a dual-concentrate, proportioning machine. Entering from the left side of the diagram product water is joined by an “acid concentrate” (the A component) and a “base concentration” (the B component) to form a final dialysate. Figure obtained from: Ledebor I. Bicarbonate in high-efficiency hemodialysis In: Bosch JP, Stein JH, eds. *Hemodialysis: High-Efficiency Treatments*. New York, NY: Churchill Livingstone Inc.; 1993: 9–26. Permission to reproduce diagram obtained from the publisher.

the sodium acetate will increase the total amount of buffer base [the sum of bicarbonate and bicarbonate precursors (i.e., acetate in this case)] in the final dialysate. When using sodium diacetate, this additional source of buffer base should be kept in mind. In the instance of citrate, being trivalent, 1 mmol of citrate is equivalent to 3 mEq of citrate. It should be noted that the function of each of the above acids is to react with an equivalent amount of sodium bicarbonate to produce carbonic acid. The combination of appropriate amounts of sodium bicarbonate and carbonic acid will provide a final dialysate pH that will assure the solubility of the divalent cations. For example, if there are a total of 39 mmol of bicarbonate/L and 4 mmol of acetic acid/L in the final dialysate to begin with, 4 mmol of the bicarbonate/L present will titrate with the 4 mmol of hydrogen/L present (derived from the 4 mmol/L of acetic acid) to produce 4 mmol of carbonic acid/L, leaving behind 35 mmol of bicarbonate/L, and 4 mmol/L of acetate intact. The 4 mmol of carbonic acid/L is equivalent to a PCO_2 of $4/0.03=133$ mmHg (as data pertaining to dialysates are not available, it is assumed that a dialysate has a solubility coefficient of carbon dioxide in the order of 0.03. This is because both cerebrospinal fluid and plasma, fluids that have properties similar to those of dialysates, share this value⁹). If one inserts the above data into Henderson's equation,

$$\begin{aligned} [H^+] &= 24 PCO_2 / [HCO_3^-] \\ &= 24 (133) / 35 \\ &= 91 \text{ nmol/L} \end{aligned}$$

where $[H^+]$ is the dialysate hydrogen ion concentration in nmol/L, PCO_2 is the dialysate partial pressure of carbon dioxide in mmHg, and $[HCO_3^-]$ is the dialysate bicarbonate ion concentration in mmol/L.

This hydrogen ion concentration corresponds to a pH of 7.04 (in reality, the final pH may be slightly higher e.g., 7.2, because of various interfering factors). Such still very low pHs will ensure the solubility of the divalent cations. These cations will have solubility problems only when the ambient pH is much higher than the above, e.g., a pH in the realm of 8.0.

It should be noted that in the above example, a modern, 3-stream, dual-concentrate, proportioning dialysis machine will indicate that there are only 35 mmol/L of bicarbonate in the final dialysate (because this is the amount that has been requested) even though 39 mmol/L of bicarbonate has been delivered to produce the final dialysate in the first place (healthcare workers need to consult their dialysis machine's manufacturers to determine if their machines have this particular property). In

addition, the final dialysate is left with 4 mmol/L of acetate, remaining after the 4 mmol/L of acetic acid have lost 4 mmol/L of hydrogen through titration with bicarbonate. Replacing the 4 mmol/L of bicarbonate that have been consumed through titration with hydrogen, these 4 mmol/L of acetate will not increase the total buffer base content of the final dialysate (in this case, a total of 39 mmol/L of buffer base consisting of 35 mmol/L of bicarbonate and 4 mmol/L of acetate). Under normal circumstances, the fraction of these 4 mmol/L of acetate that might gain access into the blood as a result of dialysis will be metabolized to generate bicarbonate in an equimolar manner. The principle underlying the fate of acetate in acetic acid in the above example also applies to the conjugate anions of the other organic acids used in "acid concentrates" in general.

It should be noted that lower dialysate bicarbonate concentrations are used to dialyze patients with metabolic alkalosis, and higher dialysate bicarbonate values to treat patients with metabolic acidosis. With modern, 3-stream, dual-concentrate, proportioning machines, the dialysate bicarbonate concentration can be varied, for example from 20–40 mmol/L, by altering the delivery rate of the "base concentrate." In order to maintain a given final dialysate sodium level, any fall in the delivery of one concentrate is compensated for by a reciprocal rise in the delivery of the other. As a result, minor changes in the final dialysate concentrations of the ingredients of the "acid concentrate" are observed when the bicarbonate level of the final dialysate is altered.

Certain dialysis machines use a batch system instead of a proportioning system to generate a bicarbonate-based dialysate. To house the dialysate, a batch system machine commonly contains a tank that is hermetically sealed to prevent the loss of carbon dioxide. The dialysate is produced by mixing an "acid concentrate," a "base concentrate," and water inside the sealed tank. The chemical principle underlying the fashioning of a bicarbonate-based dialysate in a batch system is the same as that in a proportioning system.

The bicarbonate flux from the dialysate to the patient is determined by the transmembrane concentration gradient and by the ability of the dialyzer to transfer bicarbonate (bicarbonate dialysance). In a French study of 7,123 patients, a midweek predialysis plasma bicarbonate of 22.8 ± 3.5 mmol/L was obtained when using a variety of commonly used bicarbonate concentrations in the dialysate.⁴⁵

Data advocating the use of higher dialysate bicarbonate (e.g., 40–42 mmol/L in many cases) concentrations, besides the known benefit of improved control of acidosis,⁴⁶ include improvements in protein turnover,⁴⁷ triceps

fold thickness,⁴⁸ and serum branched-chain amino acids.⁴⁹ In vivo studies in a small cohort of patients who were dialyzed with a high dialysate bicarbonate concentration (40 mmol/L) were observed to have more hypotension and hemodynamic instability.⁵⁰ Metabolic alkalosis has also been shown to increase neuromuscular excitability along with a concomitant decrease in cerebral blood flow, giving rise to paresthesias, twitching, and cramps.^{51–53}

In a study by Gabutti et al.,⁵⁴ the mean systolic, mean diastolic, and the nadir of systolic blood pressure were significantly lower with the use of a dialysate bicarbonate concentration of 32 mmol/L in comparison with those values obtained when a concentration of 26 mmol/L was used instead.⁵⁴ Furthermore, the incidence of symptomatic hypotension, silent hypotensive episodes and the need to use extra isotonic saline or hypertonic glucose infusions or both was greater in the high bicarbonate group. The heart rate was not significantly influenced by the use of the higher dialysate bicarbonate level.⁵⁴

Many studies have looked into the possibility of using lactate instead of bicarbonate as a dialysate buffer base, especially for patients receiving continuous veno-venous hemodialysis therapy.^{55–58} However, critically ill patients with acute renal failure, especially in the face of concomitant sepsis or circulatory shock have been reported to display a reduced lactate tolerance.⁵⁹ This drawback precludes the use of lactate-based dialysates in renal failure patients with concomitant hepatic dysfunction or lactic acidosis.

ACETATE (MW 59)

Among dialysates, bicarbonate-based ones are the most plasma-resembling, and most physiologic. However, in the past, the use of bicarbonate in batch systems has been associated with the precipitation of calcium and magnesium when an initially lower dialysate pH becomes more alkaline. This pH increase is because of the loss from the dialysate of carbon dioxide gas. For this reason and also because of the ease of bacterial contamination, bicarbonate was largely replaced by acetate during the later years. Use of acetate was advantageous as the chemical was inexpensive and readily converted in an equimolar manner into bicarbonate in the body. In addition, acetate possesses a bacteriostatic property. During the 1980s, with the widespread use of high-efficiency dialysis, acetate-induced side effects were often observed, especially in women.⁶⁰ The untoward effects included hypoxemia, vasodilatation, depressed left ventricular function, and impaired lipid and ketone metabolism. For these reasons

and along with the development of 3-stream, dual-concentrate, proportioning machines that can prevent or minimize the loss of carbon dioxide gas, bicarbonate has resumed its place as the dialysate buffer base of choice. However, in many dialysis centers around the world, acetate is still often being used as the principal dialysate buffer base because of its low cost and because it can be used in less expensive, single-concentrate dialysis machines.

CALCIUM (MW 40)

Even though calcium is one of the most abundant substances in the body, the plasma concentration of ionized calcium is only about 1.1 to 1.5 mmol/L. The total body calcium ranges from 1.0 to 1.5 kg (or about 1.5% of the total body weight), of which 99% is stored in the bones.⁶¹ Of the calcium in the plasma, 40% is bound to proteins (80–90% of that to albumin), 14% is complexed, and 46% is ionized.⁶² The latter 2 fractions are dialyzable. A balanced diet provides about 800–1200 mg of calcium per day, of which varying amounts are absorbed by the intestines.⁶¹

In dialysis clinics in the United States, the concentration of calcium in the dialysate is probably the most varied of all the electrolytes. The most common concentrations used today are 1.25, 1.5, and 1.75 mmol/L (i.e., 2.5, 3.0, and 3.5 mEq/L; or 5.0, 6.0, and 7.0 mg/dL). The dialysate calcium level tends to equilibrate with the ionized fraction of the plasma calcium. In the earliest days of dialysis, dialysate calcium concentrations of 1.25 to 1.3 mmol/L were commonly utilized. Soon it became evident that in order to maintain positive calcium balances, one needs to use a dialysate calcium bath of at least 1.5 to 1.55 mmol/L.⁶ Subsequently, higher calcium baths were advocated. It was observed that a calcium bath of 1.63 mmol/L or higher could lead to transient hypercalcemia with symptoms of nausea and vomiting.⁶ Also, recently, it has been shown that severe calcification of tissues is often seen in dialysis patients, which could have resulted from high intakes of calcium whether through the diet or via the dialysate.^{63–65} As we move from aluminum-based phosphorus binders to calcium-based ones to sevelamer and, most recently, to lanthanum carbonate, the total daily intake of calcium changes. Dialysate calcium values should be adjusted to reflect the effects of dietary (including calcium-containing medications) intake of calcium and also the effects of supplementation with vitamin D analogs. Calcium balance is also influenced by the amount of ultrafiltration⁶ as an ultrafiltrate contains ultrafilterable calcium, constituted

by both the ionized and the complexed fractions whose values are closely similar to those of their plasma counterparts.

Secondary hyperparathyroidism with bone disease is a common finding in dialysis patients. Even though treatment of secondary hyperparathyroidism mainly consists of the use of vitamin D analogs, manipulation of the dialysate calcium concentration can also play a role. It has been shown that the use of a calcium bath of 1.25 mmol/L is associated with a significant rise in plasma parathyroid hormone (PTH).⁷ Furthermore, a calcium bath of 1.75 mmol/L can suppress PTH secretion.⁶ The decrease in plasma PTH value induced by a high dialysate concentration of calcium may only be transient and is clearly not as strong as that induced by vitamin D.

Finally, when deciding what calcium bath to use, one needs to consider the effect of dialysate calcium level on systemic blood pressure. It has been demonstrated that the use of a low-calcium bath is associated with a mild but significant decline in the mean blood pressure during dialysis. This effect is mediated through a decrease in cardiac contractility. In fact, there is no change in systemic vascular resistance.⁸ In patients with intradialytic hypotension, a trial of using a higher calcium bath may be indicated.

Daily dialysis may have additional benefits for chronic renal failure patients. It has been shown that with daily, long, nocturnal dialysis, a calcium bath of 1.25 mmol/L will lead to a negative calcium balance. As daily, long, nocturnal dialysis is effective in removing more phosphorus, the requirement for phosphorus binders (which are usually calcium based) also decreases. The reduction in the consumption of calcium-based phosphorus binders lowers the total calcium intake. Thus, patients on frequent nocturnal dialysis often need to be dialyzed with higher calcium baths.⁶⁶ A similar situation has not been demonstrated for patients on short daily dialysis.

MAGNESIUM (MW 24)

Magnesium is the fourth most abundant cation in the human body, totaling 21–28 g, of which only 2% is in the extracellular space.⁶⁷ Sixty-seven percent of the body magnesium is stored in the bone, while another 20% is stored in muscles. The normal plasma concentration of magnesium averages at 0.8 to 0.9 mmol/L, of which only 20% is protein bound. Normal American diet entails about 10 to 15 mmol of magnesium per day. Dialysate magnesium concentrations of 0.375 and 0.5 mmol/L (i.e., 0.75 and 1.0 mEq/L or 0.9 and 1.2 mg/dL) are most frequently used.

Magnesium concentration in the dialysate is seldom manipulated. However, there are issues that affect what concentration of magnesium should be used in a dialysate. The fact that magnesium excretion occurs mainly through the kidneys and intestinal absorption of magnesium is not affected by the presence of hypermagnesemia forces us to use lower dialysate concentrations of magnesium.⁶ A conventional, thrice weekly dialysis regimen without using any magnesium in the dialysate has been found to remove approximately 31 mmol of magnesium a week.⁶ This amount is similar to that absorbed while consuming a normal magnesium diet. However, use of a magnesium-free dialysate has been associated with the occurrence of severe muscle cramps. On the other hand, use of a magnesium bath between 0.375 and 0.5 mmol/L has not led to the development of hypermagnesemia either.

Just as in the case of calcium, magnesium-based binders have been developed to treat hyperphosphatemia. The original experience with magnesium hydroxide led to hypermagnesemia (plasma level of 1.8 mmol/L) with either no or only a small decrease in plasma phosphorus concentrations.⁷ More recently, use of magnesium carbonate has been met with greater success, while combinations of magnesium-based and calcium-based binders have also been marketed. A low-magnesium bath of 0.25 mmol/L has been advocated when using a magnesium-based binder.

Finally, plasma magnesium levels can also influence PTH production, even though the effect is not as pronounced as plasma calcium levels or vitamin D administration. Acute hypermagnesemia has been shown to reduce PTH values, while hypomagnesemia has had more controversial effects. At times, it lowers the PTH level and at other times it increases the level.

GLUCOSE (MW 180)

Dextrose is glucose monohydrate (MW 198). The following discussion uses the terms glucose and dextrose interchangeably

Glucose particles account for 5 to 6 mmol/kg of a total of 287 mmol/kg in the plasma. An ideal dialysis treatment should not alter the plasma concentration of glucose in the face of normoglycemia, should remove glucose when the patient is severely hyperglycemic, and should provide glucose to the patient in the event of hypoglycemia. In recent years, dextrose (glucose monohydrate) concentra-

tions of 100 to 200 mg/dL (5–10 mmol/L) have most often been used, which seems to accomplish the above goals.⁶⁸ The fear is that a low-glucose bath will lead to an increased caloric loss, while a high-glucose bath will decrease potassium and possibly phosphorus removal. Also, a high-glucose bath may encourage bacterial and fungal growth.^{6,68}

Although the use of a glucose-free dialysate is unlikely to bring about hypoglycemia,⁶ such use may worsen hypoglycemia in patients who have other reasons to have low plasma glucose concentrations to begin with. If one uses a glucose-free dialysate, 26 to 28 g of dextrose can be removed during a dialysis session.⁶ When using dialysate dextrose levels of 182 mg/dL, there will be an uptake of glucose of 20 g.⁶ Takahashi et al.⁶⁹ used a high $\text{CO}_2/\text{HCO}_3^-$ bath enriched with 105 mg/dL of glucose to dialyze patients; the average plasma glucose level actually declined from 118.3 to 98.6 mg/dL on account of dialysis. The reason why the plasma glucose concentration fell below the corresponding dialysate value is thought to be related to the intradialytic uptake of glucose by red blood cells. The high- $\text{CO}_2/\text{HCO}_3^-$ bath is surmised to have fostered the development, within the red blood cells, of an intracellular alkalosis, which brought about an accelerated anaerobic metabolism and a heightened glucose consumption.

Two factors need to be considered when using dextrose in the dialysate. First, there may be a risk of hypertriglyceridemia when introducing dextrose in the patient. Even though one study has shown an increase in the triglyceride concentration when switching from a dextrose-free dialysate to a dextrose concentration of 455 mg/dL, this finding has not been substantiated clearly by other studies.⁶ It is unlikely that inducing hypertriglyceridemia is a concern with the currently used, low-dextrose concentrations of 100 to 200 mg/dL. The second consideration is the fear of inadequate dialytic removal of potassium. As mentioned earlier, this is because a rise in plasma glucose concentration can induce insulin production; insulin, in turn, can promote the entry of potassium into cells. In adults, dialysis using a dialysate dextrose concentration of 200 mg/dL and using a dextrose-free dialysate was able to remove potassium in the order of 72 mmol and 54 mmol per session, respectively.⁶⁹ However, in children, the above finding has not been confirmed.⁶⁸ Thus, it may be advantageous to dialyze adult patients with recurrent hyperkalemia with a lower dextrose bath.

PHOSPHORUS (MW 31)

The normal dietary intake of phosphorus is in the order of 900 mg a day. Of this, about 35% is excreted through

the gastrointestinal tract, while the kidneys excrete the remaining 65%.⁷⁰ In the event of renal failure, the gastrointestinal tract is unable to compensate for the lack of urinary removal.⁷⁰ Therefore, it is not uncommon to encounter hyperphosphatemia in the face of renal failure. Furthermore, a conventional dialysis session is only able to remove 250–325 mg of phosphorus.⁶⁴ Therefore, dialysis patients are often hyperphosphatemic, requiring phosphorus binder therapy.

Despite the high prevalence of hyperphosphatemia in dialysis patients, on occasions, one might encounter hypophosphatemia in these individuals. Severe hypophosphatemia is associated with a myriad of dysfunctions including tissue hypoxia, hemolysis, leukocyte and platelet dysfunction, rhabdomyolysis, cardiomyopathy, and muscle weakness.⁷⁰ Oral and intravenous phosphorus therapy may result in unpredictable plasma levels because of underdosing or overdosing (thus requiring frequent plasma level monitoring). Underdosing can bring about undercorrection and persistence of hypophosphatemia whereas overdosing can lead to hyperphosphatemia, hypocalcemia, metastatic calcification, hypotension, and cardiac arrhythmias. Dialyzing hypophosphatemic dialysis patients with phosphorus-enriched dialysates can not only prevent the loss of phosphorus through the use of a conventional, phosphorus-free dialysate but can also, by tailoring the dialysate phosphorus level in accordance to individual needs, introduce phosphorus into the body instead, making the targeting of postdialysis plasma phosphorus levels a much easier task. Such targeting is easier because, other things being equal, if the dialysate phosphorus level is higher than that in the plasma prior to dialysis, the postdialysis plasma phosphorus value will never be higher than that in the dialysate.⁷⁰ The often-used dialysate phosphorus concentrations have varied from 0.65 to 2.6 mmol/L, with the 1.3 mmol/L one being the most frequently used. Soluble sodium phosphates can be added to either the “acid concentrate” or the “base concentrate” of the dual-concentrate, proportioning system.⁷⁰

Hypophosphatemia is most commonly seen in dialysis patients in 2 clinical situations. First is the malnourished patient who has a very low intake of phosphorus and second is the aggressively dialyzed patient. Situations requiring aggressive dialysis include pregnancy in a renal failure woman, vancomycin toxicity, ethylene glycol poisoning, lithium intoxication, uremic pericarditis, and sepsis-induced hypercatabolism.⁷⁰ There are emerging data suggesting that long, daily nocturnal dialysis may be beneficial for patients with end-stage renal disease. Enriching the dialysate with phosphorus for patients treated with

this modality, who have a tendency to develop hypophosphatemia, is frequently practiced.¹⁸ The use of a dialysate enriched with both phosphorus and ethanol for the treatment of methanol poisoning has also been described.^{3,71}

ETHANOL (MW 46)

Since ethanol has several-fold greater affinity for the enzyme, alcohol dehydrogenase, than ethylene glycol or methanol, it can retard the breakdown of these toxic alcohols, thus allowing their removal by dialysis prior to their enzymatic breakdown with the liberation of harmful breakdown products.⁷² Because ethanol is vastly less expensive than fomepizole, ethanol use may play a large role in the treatment of poisoning by the above-mentioned toxic alcohols. In addition to the oral and intravenous routes, ethanol can be administered via the dialysate route.^{3,71} The use of an ethanol-enriched dialysate, along with intravenous ethanol administration, has been found to be helpful in the management of patients with methanol poisoning.³ A dialysate ethanol level of 100 mg/dL (22 mmol/L) is often used. Such a dialysate level ensures that the plasma value raised by the prior and concomitant intravenous administration will not fall below 100 mg/dL on account of dialysis (plasma ethanol levels between 100 and 200 mg/dL can adequately saturate alcoholic dehydrogenase activity).⁷² To obtain this level, proper amounts of 100% ethanol can just be poured into either the "acid concentrate" or the "base concentrate" of a dual-concentrate, proportioning system.⁷³

IRON (MW 56)

Iron deficiency is a common problem in hemodialysis patients.⁷⁴ Impaired absorption of iron, blood loss through the dialysis procedure, and increased requirements because of erythropoietin-stimulated erythrocyte production all contribute to at least a relative iron deficiency state.⁷⁴ Oral iron supplementation programs have failed primarily because of noncompliance in addition to the presence of gastrointestinal adverse effects.⁷⁵ Soluble iron salts are toxic for parenteral administration because the free iron released catalyzes free radical generation and lipid peroxidation.⁷⁶ Colloidal iron compounds used for intravenous administration comprise iron dextran, iron saccharate (iron sucrose), and iron gluconate. The administration of all these iron formulations can be associated with hypotension and anaphylactoid reactions.⁷⁷

In a recent *in vitro* study by Manley et al., aimed at determining the removal of iron sucrose and iron dextran by conventional, high-flux, or high-efficiency dialysis, no iron sucrose (MW 34,000–60,000) was recovered from the dialysate, and only a negligible amount of the administered dose (not more than 6%) of iron dextran (MW 90,000) was recovered from the dialysate compartment of the dialyzer, the ultrafiltration rate during the procedures being 0 to 500 mL/hr over a 4-hr treatment period.⁷⁸

Ferric iron is strongly complexed with pyrophosphate to form soluble ferric pyrophosphate.⁷⁹ Furthermore, pyrophosphate is known to trigger iron release from transferrin, enhance iron transfer from transferrin to ferritin, and promote iron exchange between transferrin molecules. Gupta et al.⁵ found that the dialysate route was safe and efficacious in the transport of ferric pyrophosphate into the blood of dialysis patients. In order for transport via a dialysate to take place, ferric pyrophosphate has to be complexed with sodium citrate first to render the resultant complex soluble in aqueous solutions. The complex is stable in a wide range of concentrations (from 2 to 70 µg/dL) that are suitable for dialytic use.⁵ Further studies are needed to determine the long-term efficacy and safety of this iron preparation.

CITRIC ACID (MW 192)

Citric acid, able to exist in a dry form, is a physiologic acid and can easily be metabolized by both subjects with no renal failure and patients with renal failure. Ahmad et al.⁴ used citric acid instead of liquid glacial acetic acid as the acid ingredient in the "acid concentrate" of a dual-concentrate, proportioning system. When using this special citric acid-containing concentrate to dialyze patients, no adverse effects were noted other than an insignificant decrement in the plasma ionized calcium level immediately postdialysis. This decrement normalized itself almost completely after 1 hr. The decline was more pronounced when using a dialysate with a calcium concentration of 1.25 mmol/L compared with the time when a concentration of 1.5 mmol/L was used. No increase in bleeding episodes was noted in any of the patients studied. Furthermore, there was an increase in the dialysis dose delivered to patients in the citrate arm of the study, which the authors postulated as being a local anticoagulant effect at the blood side of the dialyzer membrane. Even though the dose of citrate used was lower than that normally needed for anticoagulation, the authors conjectured that the anticoagulant effect of citrate might have helped preserve the dialyzer membrane permeability

better, leading to a higher clearance for urea.⁴ Confirmation of the study results is being awaited.

UREA (MW 60)

If a patient's plasma urea concentration is high prior to dialysis, there is a risk of developing the dialysis disequilibrium syndrome¹⁴ if an aggressive dialysis treatment is carried out. One way to prevent this problem is to enrich the dialysate with urea. Doorenbos et al.¹ reported a patient for whom introducing an appropriate quantity of urea into the dialysate successfully prevented the occurrence of this syndrome.

ULTRAPURE DIALYSATE

Soon after hemodialysis became a standard treatment for end-stage renal disease, it was realized that high bacterial counts in the dialysate could cause pyrogenic reactions.⁸⁰ The Association for the Advancement of Medical Instrumentation (AAMI) sets quality standards for dialysate purity. The most recent recommendations require dialysates to have less than 200 CFU/mL of bacteria and less than 2 EU/mL of endotoxins.⁸¹

In recent years, chronic inflammation has been implicated to be able to bring about unsatisfactory outcomes in patients afflicted by many chronic diseases including those patients maintained on dialysis.^{80,82–84} It has been suggested that the presence of high levels of bacteria and of endotoxins in the dialysate can pave the way for a substantial degree of inflammation to occur.^{80,82–84} In this regard, recent studies have shown that, in many dialysates, there are proinflammatory bacterial fragments, some of which can be detected by the silk worm larvae plasma test.⁸³ In addition, some of these bacterial fragments may be as small as 1,250 daltons and can pass through the dialyzer membrane to reach a patient's blood.⁸⁵ The criteria for an ultrapure dialysate include a maximum bacteria level of 0.1 CFU/mL and a maximum endotoxin level of 0.03 EU/mL.^{80,84,86} The European Renal Association now strongly recommends the use of ultrapure dialysates.⁸⁵ Use of ultrapure dialysates has been reported to lead to lower plasma levels of C-reactive protein and interleukin-6.⁸⁰ In one study, after 1 year of dialysis using ultrapure dialysates, patients showed increases in plasma albumin value, estimated dry body weight, and protein catabolic rate when compared with similar parameters observed during standard dialysis.⁸⁰ In addition, another study was able to demonstrate an ability to reduce the cumulative dose of erythropoietin with the use of ultrapure dialysates.⁸⁰

Normally, the water for making a dialysate is first purified by a combination of exposure to a water softener, passage through a charcoal filter, reverse osmosis, exposure to deionizers, and passage through an ultrafilter and other filters. Most of the time, the breakdown in bacterial exclusion occurs after water destined for dialysate preparation has been purified and is on its way to the dialysis machine.⁸⁰ Safeguards are required to ensure the ultrapurity of an ultrapure dialysate. These safeguards include selecting a minimum length of piping, not using storage tanks, and, possibly, the interposition of an ultrafilter immediately distal to a storage tank if one is used. The "acid concentrate" is usually not a source of contamination because of its low pH while the "base concentrate" can be a source of bacterial contamination because of its ability to provide a good environment for bacterial growth. Thus, special care should be taken to avoid bacterial contamination of the "base concentrates." In order to transform into an ultrapure dialysate, a conventional dialysate needs to pass through a final ultrafilter prior to entry into a dialyzer.^{80,84}

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