Acid–base homeostasis with the high convective dialysis treatments

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Abstract
The feedback between metabolic acid production and dialytic base gain ensures a neutral acid–base balance in patients on renal replacement therapy (RRT). Despite acid not accumulating continuously, clinical studies demonstrated that normalizing pre-dialysis serum bicarbonate results in nutritional and osteodystrophy improvements. Full correction of acidosis is not an easy task in dialysis patients because it depends on both some intrinsic characteristics of patients and dialysis prescriptions. Thus, a large variation in the result is often recorded among dialysis populations and in acid–base studies. Highly convective dialysis treatments make the individualization of dialytic parameters easier than conventional dialysis. Up to now, few clinical data have been published. However, knowledge of and the quantification of the kinetic phenomena that govern the buffer transfer during a session of these high performance treatments can provide a rational approach to the optimal dialysis prescription.

Keywords: acidosis; bicarbonate; convection; diffusion; haemodialfiltration; haemodialysis; haemofiltration

Introduction
Maintenance of acid–base homeostasis requires day-to-day replenishment of the alkali consumed in neutralizing the acids produced by endogenous metabolic processes and the alkali lost in urine and stools. In patients with functioning kidneys, alkali stores are replenished by renal acid excretion, a process that generates new bicarbonate in the body. In patients without functioning kidneys, alkali restoration is accomplished by the addition of either bicarbonate itself or a metabolic precursor of this anion, such as lactate or acetate.

In renal replacement therapy (RRT), patients’ serum bicarbonate value is often lower than the normal range in a healthy population, while the pH is in the normal range or only slightly reduced because of adaptive hypocapnia. Although dialysis incompletely corrects acid–base homeostasis, it seems that the acids produced by metabolism do not accumulate continuously because an equilibrium between alkali addition with dialysis and metabolic acid production occurs [1]. In vivo studies provided evidence that RRT patients are in a day-to-day acid balance [2]. Nonetheless, it has been demonstrated that in dialysis patients, the lower than normal serum bicarbonate worsens metabolic bone disease [3] and affects protein and amino acid metabolism [4,5]. Thus, it is still a matter of debate which level of serum bicarbonate is desirable in RRT patients.

Clinical effects of ‘normal serum bicarbonate’
During continuous therapies [continuous ambulatory peritoneal dialysis (CAPD) and continuous arteriovenous haemofiltration (CAVH)], the continuous buffer flux toward the patient continuously offsets the metabolic acid production and, consequently, a stable serum bicarbonate is normally recorded. In standard, thrice weekly intermittent therapies [haemodialysis (HD), haemofiltration (HF) and haemodiafiltration (HDF)], this parameter fluctuates from a maximum concentration just after the end of the session to a minimum level before dialysis. In these conditions, it is hard to define the ‘true’ acid–base correction [6]. All studies refer to the pre-dialysis serum bicarbonate even though this value only roughly reflects the acid–base status for the majority of the interdialytic period.

In one controlled prospective study [3], patients with a serum bicarbonate restored to normal (24.0 ± 0.61 mmol/l) by adding additional HCO₃⁻ to the bath solution had a smaller increase in parathyroid hormone (PTH) levels over an 18 month period of observation.
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when compared with a group of patients with no correction of acidosis (15.6 ± 1.0 mmol/l). Strikingly, correction of acidosis not only decreased the bone turnover in high-turnover (i.e. hyperparathyroid) osteodystrophy (documented by bone biopsies and osteocalcin measurements), but also improved the bone turnover in low-turnover bone disease (unrelated to hyperparathyroidism). In a second study, correction of acidosis in HD patients improved the sensitivity of PTH to calcitriol [7].

The problem with these seemingly straightforward observations is that bone calcium stores are insufficient to buffer the retained acid for longer than 6 months to 1 year [8,9]. A major issue is whether the patients were in acid–base balance. Unfortunately, acid–base balance is difficult to measure, and small errors could lead to false conclusions [9]. However, it has been demonstrated [10] that also in patients without chronic renal failure and in apparent neutral acid–base balance, the administration of potassium bicarbonate reduced bone reabsorption and increased bone formation. The authors hypothesized that the normal Western diet imposes a chronic acid load which may produce a very low-grade and transient metabolic acidosis. The implication of this study is that the metabolic acid production can contribute to the genesis of bone disease even if acid–base balance is apparently neutral [11].

Two randomized studies in HD patients on nutritional parameters have resulted in opposite conclusions: Brady and Hasbargen [12] did not find any effect on serum albumin and total lymphocyte count, taken as nutritional markers, in two groups of patients treated with a high and a low bicarbonate concentration despite a significant difference in predialysis arterialized bicarbonate (17.3 ± 3.2 and 20.2 ± 2.9 mmol/l, respectively). In contrast, Williams et al. [4] found a significant increase in triceps skin fold thickness associated with an increase in predialysis arterialized total CO2 when patients were treated with the high bicarbonate dialysate (from 22.5 ± 3.2 to 26.7 ± 3.9 mmol/l). This beneficial effect was then reversed by resuming the standard bicarbonate dialysate.

The major differences in these two studies were the levels of serum bicarbonate achieved: despite an improvement, the serum bicarbonate concentration in the study by Brady was far from the normal range (25.2 ± 1.0 for arterialized bicarbonate [13]), while in the second study a substantial number of patients achieved the normal range (26.4 ± 1.0 for arterIALIZED total CO2 [13]). In a cross-sectional analysis in 81 patients, Movilli et al. [5] found a significant detrimental role of acidosis on serum albumin concentration: patients with normal pre-dialysis serum bicarbonate (>23 mmol/l) showed a serum albumin concentration of 4.18 ± 0.31 g/l, while in the group with serum bicarbonate level <20 mmol/l, the mean serum albumin was 3.96 ± 0.22 g/l. This effect was independent of protein intake as evaluated by protein catabolic rate.

These data support the view that the target for acid–base correction in dialysis patients should be the normal value for the healthy population. This value is, however, difficult to achieve in the majority of patients treated with RRTs.

Two groups of factors influence serum bicarbonate in all RRTs, one is related to the patient and the other to the dialysis schedule.

Dialysis with fixed parameters results in different bicarbonate serum levels in different patients because metabolic acid production and the distribution space for bicarbonate are individual characteristics. In a single patient, different dialysis schedules result in different levels of serum bicarbonate [6]. These two reasons explain the different results found in various acid–base studies. The calculated differences [14–17] between different dialysis schedules in a given patient are depicted in Figure 1.

Factors affecting serum bicarbonate in conventional dialysis

In the diffusive treatments such as conventional HD, the bicarbonate transfer during the session is determined mainly by the diffusive gradient between the serum bicarbonate and the dialysis fluid bicarbonate concentration. While at the beginning of the session this gradient is maximal, during dialysis it declines due to the contemporaneous increase in serum bicarbonate that, in turn, depends on the bicarbonate transfer from the dialysate [18]. Late during the treatment, the bicarbonate flux could cease if the gradient is dissipated. It is evident that the bicarbonate concentration in the dialysis fluid determines the level of this equilibration. Distribution space for bicarbonate also influences the achievement of equilibrium: patients with a low distribution space readily increase serum bicarbonate concentration, while in a high distribution space patients, bicarbonate flux is diluted and the serum bicarbonate only increases slowly, thus allowing more bicarbonate to be gained. However, if the bicarbonate availability in the dialysis fluid is sufficient for saturating...
a wide range of bicarbonate distribution spaces during the time of the dialysis session, post-dialysis serum bicarbonate levels could be virtually identical in a large number of patients. Ottinger et al. [16] demonstrated that in patients with a high post-dialysis serum total CO₂, the increase in the dialysate buffer concentration had no effects on post-dialysis serum total CO₂ as compared with the lower dialysate buffer content.

A further mechanism contributes to the inter-individual variability of acid–base homeostasis: the rapid addition of alkali during dialysis could stimulate the production of organic acid as a defence mechanism against alkalosis. The hydrogen ion generated consumes the infused bicarbonate, while the organic anion is lost with the dialysate [18]. However, no studies have quantified the size of this phenomenon.

During the interdialytic period, serum bicarbonate decreases both by dilution (alkali-free fluid retention) and by metabolic acid production. The individual acid production determines the level of the pre-dialysis serum bicarbonate. The concept of neutral balance in dialysis is based on the fact that pre-dialysis serum bicarbonate inversely correlates with the bicarbonate transfer during the session: when it is low, the diffusive gradient is high and consequently the buffer transfer is high, and when it is high, the transfer is reduced [1]. The low pre-dialysis serum bicarbonate reflects a high metabolic acid production that is counterbalanced by a high bicarbonate transfer during dialysis. A high pre-dialysis serum bicarbonate reflects a low metabolic acid production that is counterbalanced by a low bicarbonate transfer during dialysis. In stable metabolic conditions and with a constant dialysis schedule, the pre-dialysis serum bicarbonate level is constant in individual patients.

Ultrafiltration reduces pre-dialysis blood bicarbonate by reducing the dialytic base gain [14]. It could be calculated theoretically that 1 l of fluid removal reduces the dialytic base gain by ~20 mmol/session. Although these convective losses do not change the serum bicarbonate concentration during dialysis, the subsequent retention of an equivalent amount of alkali-free fluid in the interdialytic period does. In a crossover study of 29 patients, Fabris et al. [19] found that by reducing the interdialytic weight gain of 1 kg, pre-dialysis blood bicarbonate significantly increased by 1.6 mmol/l.

Several investigators have modelled the process of bicarbonate transfer to the patient during treatment, but it is clear that only by individualizing the bicarbonate dialysate concentration could an optimal correction be achieved. Some studies have demonstrated that increasing the bicarbonate content in the bath increases the mean pre-dialysis serum bicarbonate in the dialysis population [16,20].

In this way, the diffusive gradient increases and the equilibration occurs late or does not occur during the session. This procedure, however, could expose some patients, mainly those with a low distribution space for bicarbonate, to a post-dialysis alkalosis.

Acid–base balance in haemofiltration and haemodiafiltration

In treatments with a high convective component buffer, gain is provided totally or partially by a substitution solution which contains a buffer (bicarbonate or lactate). The modern form of these treatments uses on-line preparation of the substitution solution instead of pre-formed sterile bags used in the past. Buffer kinetics are substantially different from conventional diffusive dialysis and differ also between pure convective HF and mixed convective and diffusive HDF. The mode of substitution fluid administration, before the filter (pre-dilution) or after the filter (post-dilution), is also important for the final acid–base balance.

The general concept of the neutral balance and the feedback between dialytic base gain and metabolic acid production is still preserved, but the pre-dialysis serum bicarbonate level achievable and the possible interventions for normalizing it are still not completely explored.

In post-dilution HF, the bicarbonate contained in the removed plasma water is replaced by the bicarbonate contained in the substitution fluid. The difference between these concentrations multiplied by the amount of ultrafiltration is the net buffer administered to the patient. As in the diffusive treatments, serum bicarbonate increases during the session, thus reducing the net transfer of buffer. The final balance depends on the distribution space for bicarbonate, on the buffer concentration in the substitution fluid and on the amount of ultrafiltration. Since the ultrafiltration rate in this HF mode is relatively low, the first two factors are the most important.

A clinical study [21] comparing different bicarbonate concentrations in the substitution fluid (30, 35 and 40 mmol/l) showed that the serum bicarbonate post-dialysis value was directly correlated to the bicarbonate concentration in the fluid.

In pre-dilution HF, the dialysis fluid is mixed with plasma water and thus the bicarbonate removed with ultrafiltration results from this mixture. The main variability depends both on the rate of fluid infusion and on the bicarbonate concentration of the fluid. In recent studies [22,23] when pre-dilution HF with high ultrafiltration (19 l/h) and high total buffer-containing dialysate (36.5 mmol/l) was compared with HD with the same total buffer-containing dialysate, a mild but significant increase in pre-dialysis serum bicarbonate was recorded (HD 21.8 and HF 22.8 mmol/l). HF with a lower ultrafiltration (18 l/h) and a lower buffer concentration in dialysis fluid (34.5 mmol/l) was not different from HD in acid–base status (HD 20.2 and HF 19.6 mmol/l).

In HDF, the interplay between diffusion and convection makes the buffer kinetic evaluation particularly complex. When convective bicarbonate flux is in the opposite direction to the conventional diffusive flux, some solvent–solute interactions occur which limit the
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Table 1. Changes in base gain and in pre-dialysis blood bicarbonate with different haemodiafiltration schedules

<table>
<thead>
<tr>
<th>Bath</th>
<th>Buffer flux (mmol/min)</th>
<th>Pre-dialysis $\text{SHCO}_3$ (mmol/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bath = Acetate 38</td>
<td>0.66</td>
<td>16.5 ± 2.2</td>
</tr>
<tr>
<td>Bath = Acetate 38 Substitution = Lactate 40</td>
<td>1.16</td>
<td>17.7 ± 2.3</td>
</tr>
<tr>
<td>Bath = Bicarbonate 50</td>
<td>1.56</td>
<td>18.6 ± 3.3</td>
</tr>
<tr>
<td>Bath = Bicarbonate 35, Acetate 4 Substitution = Lactate 40</td>
<td>2.06</td>
<td>21.0 ± 2.1</td>
</tr>
<tr>
<td>Bath = Bicarbonate 35, Acetate 4 Substitution = Bicarbonate 50</td>
<td>2.06</td>
<td>21.0 ± 2.1</td>
</tr>
</tbody>
</table>

$^a$Calculated from [15].
$^b$From [24].

diffusive entry of small molecules against a high convective current [15]. In a relatively low ultrafiltration schedule (3 l/h), endogenous bicarbonate is lost even when the transmembrane gradient should allow a bicarbonate gain from the dialysate: multiple linear regression predicted that the diffusive bicarbonate flux is positive (toward the patients) only when the transmembrane gradient is $>15\text{mmol}$ [15]. The buffer concentration in the substitution fluid plays a key role in determining the final balance and, consequently, the pre-dialysis serum bicarbonate. Table 1 reports a summary of some studies in which both kinetics and clinical results are presented [15,24].

When on-line HDF is used in the post-dilution mode, the high convective transfer increases the endogenous bicarbonate loss with dialysate despite a positive gradient, but the concomitant very high buffer infusion with the substitution fluid allows a bicarbonate-positive net balance even if the total buffer content (bicarbonate + acetate) in the fluid is relatively low (33 mmol/l) as compared with the lower ultrafiltration HDF [25]. A short-term study in a few patients showed that pre-dialysis and post-dialysis serum bicarbonate levels were almost identical to those of high flux HD [26].

Interestingly, pre-dilution HDF resulted in a lower net buffer balance as compared with post-dilution HDF: during this dialytic procedure, the infusion of a solution with a bicarbonate concentration higher than that of serum before the filter increases the bicarbonate concentration of the blood entering the filter [25]. In this condition, there is virtually no diffusive bicarbonate gradient, thus increasing the bicarbonate losses with dialysate. In order to compensate for this phenomenon, Pedrini et al. [25] suggested increasing the bicarbonate content in the dialysate. Also in a clinical setting, it seems that pre-dilution HDF could result in lower pre-and post-dialysis serum bicarbonate as compared with post-dilution HDF.

Conclusions

Despite no firm evidences existing showing that full normalization of pre-dialysis acid–base status in dialysis patients is associated with clinical benefits, some clinical findings seem to suggest that it is prudent to try to achieve this target. The pre-dialysis serum bicarbonate depends on patient parameters and dialysis schedules, and consequently an individualized prescription is necessary to achieve the target in all patients. In the high convective treatments, the modulation of the dialysis fluid buffer concentration, ultrafiltration rate and mode of substitution fluid infusion can be done easily with the actual modern treatments. Since profound differences in buffer kinetics between conventional HD and these new ‘extreme’ techniques occur, a careful evaluation of the acid–base status of patients should be performed when switching patients from HD to these new modalities.

References