Acid–base correction and convective dialysis therapies

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Abstract  Whichever dialysis therapy is used, there is a similar need for correcting the acid–base balance. The most important tool for this is the buffer in the dialysis fluid and, when using convective therapies, also in the substitution solution. The buffer source in all modern versions of these therapies should be bicarbonate. The more efficient the dialysis treatment in terms of small solute transport, the more rapid the uptake of buffer. Thus, optimally applied haemodiafiltration has the potential for the largest buffer gain. The target for acid–base correction in dialysis is to maintain patients within or as close to the physiological plasma bicarbonate range as possible. However, cross-sectional studies of acid–base status among patients treated with contemporary forms of dialysis often show moderate acidosis. As metabolic acidosis has been found to be an important stimulus for protein catabolism in experimental studies, an association with nutritional problems has been sought in dialysis patients. This has revealed a negative correlation between plasma bicarbonate and nutritional parameters. Acidotic patients were found to have better nutritional status than patients with normalized acid–base balance. However, caution should be exercised when interpreting plasma bicarbonate levels, since acidosis may be a cause as well as an effect of excessive protein catabolism. Although available clinical data suggest that the catabolic effect of mild acidosis can be compensated by adequate nutrition and adequate dialysis, it should be desirable to aim for a normalized acid–base balance in combination with adequate nutritional intake and delivery of dialysis.

Key words: acidosis; bicarbonate; convection; haemodiafiltration; haemofiltration

Introduction

Maintaining the acid–base balance in the body is one of the major functions of the kidney and as such should be replaced by dialysis in end-stage renal disease patients. This is achieved by including a buffer in the dialysis fluid, but the choice of buffer source and mode of dialysis are important determinants for the acid–base correction. As acidosis has been shown to affect several metabolic processes in the body, there is general agreement that it should be avoided, but the target for correction is still subject to discussion.

Components of acid–base correction in dialysis

The buffer gain during a dialysis treatment should be sufficient to compensate for the generation of acid during the interdialytic period and also for any loss of buffer that takes place during dialysis. The uptake of buffer during dialysis serves not only to increase the plasma bicarbonate level, but also to restore the buffering capacity of other body buffer systems. If the patient has been in positive hydrogen balance, his non-bicarbonate buffer stores may have contributed buffer equivalents and need to be regenerated [1]. This can be seen as an extended bicarbonate distribution space [2].

When bicarbonate is used as buffer in the dialysis fluid, the uptake is determined by the mass transfer rate across the membrane. Increasing the efficiency of dialysis, in terms of small solute clearance, leads to increased rates of transfer of bicarbonate into the blood. However, it is the difference in concentration between blood and dialysis fluid that makes up the driving force for the transport and, when the gradient is reduced gradually by rising blood bicarbonate levels, the system approaches a steady state. The titration of non-bicarbonate buffer stores still proceeds and therefore the treatment time is of importance for the total uptake of buffer. When the buffer source is acetate or lactate, which need to be metabolized before being effective as buffers, the rate of metabolism may be the limiting step and large amounts of bicarbonate may be lost from the blood before steady-state conditions are reached and there is a net gain of buffer [3].

In the various extracorporeal dialysis therapies, buffer is administered by different routes. In haemodialysis (HD), the buffer in the dialysis fluid diffuses across the membrane along a concentration gradient.
In haemodiafiltration (HDF), there is buffer in the dialysis fluid and additionally in the substitution solution, which is introduced directly into the blood. In haemofiltration (HF), buffer is provided only via the substitution solution. Looking specifically at the convective therapies, HDF and HF, there are again differences affecting the buffer administration (Figure 1). In classical HDF, which is HDF with substitution solution provided from bags with sterile fluid, the buffer in the dialysis fluid is bicarbonate, while in the substitution solution it is most commonly lactate. In the modern form of HDF which incorporates on-line preparation of the substitution solution, bicarbonate is the buffer in both fluids. Classical HF can be defined as post-dilution with externally provided fluid in bags and it is performed mainly with lactate as buffer source. In modern HF, the substitution solution is prepared on-line, it contains bicarbonate and is usually administered in pre-dilution mode.

When assessing the effect of these dialysis therapies on the acid–base correction, the major factors that contribute to a difference in buffer balance are thus the treatment efficiency in terms of small solute clearance, the choice of buffer source and the actual buffer concentration in the fluids. When performed under optimal conditions at the same blood flow rate, HDF provides the highest and HF the lowest small solute clearance (Figure 2). The order is the same for the buffers, although the direction of transport is reversed, but the buffer source determines whether the effect is positive or negative on the buffer balance. For bicarbonate, it is positive; the higher the clearance the larger the buffer gain. For acetate and lactate, it is negative; the higher the efficiency the more buffer is lost initially from blood.

**Acid–base correction in HDF—clinical result**

With the large number of variable treatment parameters in HDF, it is difficult to compare results and draw conclusions from clinical studies. The group in Vicenza addressed the choice of buffer in a well-structured study and compared classical HDF using four different buffer combinations with HD using bicarbonate [4]. For the correction of the acid–base balance as well as for the reduction of intradialytic symptoms, it was found to be more important to have bicarbonate in the dialysis fluid than in the substitution solution, but the best result was obtained when bicarbonate was used in both fluids. Optimal correction of the acid–base balance was not achieved with any mode, and the authors concluded that this would have required higher bicarbonate concentration in the fluids. In this study, the amount of convective transport was modest and this may explain why the diffusive bicarbonate transport from the dialysis fluid was more important than the convective transport from the substitution solution.

With modern HDF, the contribution of diffusion and convection, respectively, can be optimized and the bicarbonate concentration in the fluid can be individualized to achieve the desired correction of the acid–base balance. Canaud summarized his long experience of on-line HDF by reporting 12 months data for a group of 56 patients [5]. The double-pool urea Kt/V was 1.55, the normalized protein catabolic rate (nPCR) was 1.12 g/kg/day and the plasma bicarbonate levels were 22.8 mmol/l pre-dialysis and 29.9 mmol/l post-dialysis. To avoid post-dialysis alkalosis, the bicarbonate concentration in the fluid had to be reduced from 39 to 35 mmol/l after an initial period of 6–9 months. As no other change is reported, the reduced buffer need indicates generally reduced acid production, which could be a consequence of the normalized acid–base status, or that previously depleted body buffer stores are now refilled.

**Acid–base correction in HF—clinical result**

During the 1980s and early 1990s, lactate was generally used as buffer source in HF treatments. Two early
reports of post-dilution HF with bicarbonate compared the acid–base balance in patients treated first with lactate and then with bicarbonate in the substitution solution [6,7]. In both studies, higher plasma bicarbonate values could be demonstrated with bicarbonate, but only when the bicarbonate concentration in the fluid exceeded the lactate concentration with which it was compared. These studies illustrate that in classical HF the small solute clearance is so low that the transport of lactate becomes the rate-limiting step rather than the metabolism, and therefore the impact of the choice of buffer is less.

The importance of the buffer concentration on the net buffer balance was illustrated in a study from Bologna, where the concentration of bicarbonate in the substitution solution was increased in steps from 30 to 40 mmol/l [8]. The net gain of buffer was related directly to the bicarbonate concentration.

In modern HF, the efficiency of small solute removal is increased by pre-dilution, and with the use of bicarbonate in the fluid this has a positive effect on the buffer uptake. The substitution solution can be individualized to the patient’s need, regarding composition as well as volumes used.

Effects of metabolic acidosis in dialysis patients

Metabolic acidosis has been studied extensively in experimental animals and in humans and found to be an important stimulus for protein catabolism. In the acidotic state, branched-chain amino acids and muscle protein are degraded in a process where glucocorticoids play an important role [9]. In renal failure patients, the chronic exposure to acidosis could thus have serious metabolic consequences and contribute to malnutrition [10]. The widespread adoption of bicarbonate as buffer in dialysis was brought about by demands for increased dialysis efficiency, but also made it possible to increase the plasma bicarbonate levels by providing more buffer during dialysis [1]. During the 1990s, normalization of the acid–base balance became an additional goal for adequate dialysis. Prospective studies have now shown that normalizing the acid–base balance leads to metabolic changes that reverse the deleterious effects of the previous acidosis. Protein degradation decreased in patients on HD as well as on continuous ambulatory peritoneal dialysis (CAPD) when the metabolic acidosis was corrected [11,12]. Long-term studies resulted in significantly improved nutritional parameters such as increased triceps thickness, midarm muscle circumference and body weight [13,14]. There was also improvement in morbidity, with fewer days spent in hospital among patients with normalized acid–base balance [14].

To determine the clinical importance of metabolic acidosis in the dialysis population, the degree of acidosis has been correlated with signs of malnutrition. Looking at the baseline status of the first 1000 patients entering the HEMO study, the total carbon dioxide (CO₂) was found to be negatively correlated to the nPCR [15]. If PCR is interpreted traditionally as a surrogate for protein intake, this would indicate that a normalized acid–base balance is connected with reduced protein intake. A similar relationship between plasma bicarbonate and PCR was reported previously from other cross-sectional analyses of HD patients [16,17]. However, one of these studies showed a positive correlation between plasma bicarbonate and the albumin level [17]. This result stimulated a subsequent cross-over study where patients were changed from a slightly acidotic state to a normalized acid–base balance by oral administration of buffer [18]. The change in acid–base status resulted in significantly reduced PCR and increased albumin levels. The new acronym for PCR, PNA which stands for protein equivalent of nitrogen appearance, shows more correctly that it indicates the amount and not the process by which urea nitrogen is produced. In an acidotic patient, there is likely to be degradation of internal as well as external protein sources, and both are included in the PCR term. When the acidosis is corrected, the endogenous breakdown should disappear, which improves the nutritional status and reduces the PCR. We could therefore say that the PCR value connected with a normalized acid–base status is the ‘normal’ PCR.

It is clear that acidosis contributes to increased PCR, but we need also to consider the reverse; that a large protein intake gives a high PCR and contributes to acidosis. When we look at the plasma bicarbonate level in the body, we should apply a model similar to that which we apply to urea kinetics (Figure 3). The urea level in the body is affected both by generation from protein breakdown and by removal by dialysis, assuming no kidney function. Therefore, a low BUN indicates either low generation due to low protein intake or large removal by dialysis. Looking only at the BUN value does not tell us which, as we know from urea kinetic modelling. In a similar way, the bicarbonate in the body is determined by uptake during dialysis and by regeneration of body buffers (Figure 3).

A low plasma bicarbonate can thus result from either low uptake during dialysis or large regeneration of urea in the body

\[ \text{urea} \text{in the body} \]

\[ \text{removal by dialysis} \]

\[ \text{generation from protein breakdown} \]

\[ \text{bicarbonate} \text{in the body} \]

\[ \text{regeneration of buffer} \]

\[ \text{uptake during dialysis} \]

Fig. 3. Single-pool models for urea and bicarbonate in the body, assuming no kidney function.
body buffers, a consequence of a large production of acid from a large intake of protein. For dialysis patients, it is as important to determine whether their acidosis results from poor buffer uptake or large protein intake, as it is to know whether their low BUN is due to good dialysis or poor dietary intake.

A survey of laboratory data from 12,000 dialysis patients showed that the risk of death and of metabolic acidosis increased with increasing serum bicarbonate concentration, treatment etc. Patients within or as close to the physiological plasma bicarbonate level was probably connected with a low protein intake and these patients may therefore have been at risk because of malnutrition. Patients with CO2 values in the range of 17.5–20, although acidotic, were not exposed, to an increased risk of death. It is possible that the acidosis in many of these patients was caused by excessive protein intake which protected them from the catabolic effects.

The effect of acidosis on bone resorption has been demonstrated in cell cultures and experimental animals, but only a few studies have extended the observations to large groups of dialysis patients [20]. A French study from the early 1990s [21] showed that the progression of hyperparathyroid bone disease was significantly delayed when the acid–base balance was normalized. One reason for the weak evidence for a beneficial effect of normalized acid–base balance on bone disease in chronic renal failure patients could be the complexity of the disease in these patients, where disturbances in the calcium–phosphate–vitamin D–parathyroid hormone balance are likely to obscure the impact of most other factors.

General recommendations for acid–base correction

The target for acid–base correction is to maintain patients within or as close to the physiological plasma bicarbonate range as possible. The buffer uptake during dialysis can be modified by changes in buffer concentration, treatment efficiency and time, all of which can be achieved easily in modern forms of dialysis. Pre-dialysis acidosis is a sign of insufficient availability of buffer during the interdialytic period. Correcting this by increasing the buffer uptake during dialysis might lead to post-dialysis alkalosis, which should be avoided as alkalosis may be as detrimental as acidosis. To achieve a more even acid–base status, oral base supplement could be used during the interdialytic period.

The ambiguity of plasma bicarbonate levels and PCR values and their impact on nutrition have raised questions about the value of acid–base correction [22]. Although there is general agreement that severe metabolic acidosis should be corrected, it is also felt by some nephrologists that adequate protein intake and adequate dialysis could compensate for a certain degree of acidosis. Still, aiming for a normalization of the acid–base balance by using all the tools available to us today should be the preferred approach, rather than accepting a certain catabolism whose effect on various body systems presently is unknown.

References