Acid production and base balance in patients on chronic haemodialysis

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ABSTRACT

Acid generation and elimination processes were compared with total base (bicarbonate plus metabolizable anions) turnover in 18 anuric patients undergoing post-dilutional haemofiltration. The study was conducted during the second haemodialysis session of the week by means of a whole-body base balance technique. The results showed that the mean rates of base loss and base gain during dialysis did not differ (i.e. the dialysis base balance approximated to zero). The concurrent mean rate of intestinal base absorption was $66 \pm 26$ mmol/2 days, as calculated from the whole-body balance of the various inorganic cation and anion differences in a metabolic steady state. This level of intestinal base absorption would be capable of neutralizing the $59 \pm 21$ mmol of $H^+$ ions/2 days that is contributed by sulphuric acid, which is the most important endogenous acid produced in anuric patients. In spite of the fact that intestinal base supply was adequate to neutralize endogenous acid production completely, our patients presented with pre-dialysis non-carbonic acidosis. The depression of plasma bicarbonate levels could not, however, be explained by increased concentrations of the anion gap and organic acids, which were within normal limits both before and after dialysis. We suggest as an alternative hypothesis that this pre-dialysis acidosis may represent an isotonic dilution acidosis that is induced by the ingestion of base-free tap water in order for plasma tonicity to be protected from the accumulation of impermeant dietary solutes, which takes place during the interdialysis period in anuric patients.

INTRODUCTION

The anuric patient represents a closed biological system in terms of the elimination of non-metabolizable acids and bases. Such bases are disposed of exclusively by the kidney, which controls their plasma concentrations. On the other hand, carbonic and metabolizable acids continue to be eliminated through the same pathways as in subjects with normal renal function [1,2]. As compared with continuous peritoneal dialysis (CAPD), intermittent extracorporeal dialysis is characterized by the interdialytic consumption of base-free tap water and by diet-induced solute accumulation. The intestinal absorption of bases in anuric patients cannot be evaluated from

Key words: acid production, base balance, dilution acidosis, haemodialysis.

Abbreviations: AG, anion gap; $A^-_{m}$, metabolizable anions; $A^-_{nm}$, non-metabolizable inorganic anions; BE, base excess; BW, body weight; CAPD, continuous peritoneal dialysis; $C^-_{nm}$, non-metabolizable inorganic cations; NB, total base; $P_{CO_2}$, partial pressure of $CO_2$; t$CO_2$, total $CO_2$; TA, titratable acidity; TB, titratable basicity; $tP$, total phosphorus; $V_d$, extracellular volume of dry body weight.

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the urinary elimination of inorganic electrolytes using the inorganic cation–anion difference technique, as described by Oh [3]. The measurement of intestinal base absorption from electrolyte balances has not been attempted in haemodialysis patients, mainly due to the difficulty in performing reliable balance measurements with the large volumes of inflow and outflow dialysis solutions [4]. A reliable measure of intestinal base absorption has been obtained in CAPD patients with the cation–anion difference technique mentioned above, using a much slower turnover of peritoneal fluid [5,6].

Endogenous acid generation involves the production of non-metabolizable acids, pre-eminently sulphuric acid, and metabolizable acids, the acidifying effect of which is conditioned by the continuous elimination of their conjugate anions, leaving behind H+ ions in the body [7]. Whereas in subjects with urine excretion or on CAPD treatment the production of metabolizable acids is accompanied by the continuous loss of their conjugate anions [5], in anuric patients on intermittent haemodialysis no loss of metabolizable anions takes place during the interdialytic period [8]. As a consequence, the rate of endogenous acid production is greatly reduced [4,8]. Under these conditions it is sulphuric acid and other non-metabolizable organic acids that are likely to contribute to acidosis [4]. Moreover, this decreased generation of metabolizable acids may be re-inforced by even lower sulphuric acid production, compared with that contributed by an unvarying rate of protein catabolism in normal subjects [5,6,9,10].

In this context, it is not unreasonable to hypothesize that the intestinal absorption of bases may match the concurrent endogenous acid production, giving rise to neutrality. Obviously, other factors must therefore come into play to explain the pre-dialytic non-carbonic acidosis that is observed in anuric patients undergoing haemodialysis. For example, little attention has been paid to the dialysis-induced loss of metabolizable anions, which is capable of nullifying the dialysis-induced bicarbonate gain. Moreover, the role played by the ingestion and retention of base-free tap water, as an acidifying factor, has so far been neglected [4].

Thus, in order to clarify the nature of pre-dialysis acidosis, we investigated the following aspects: (1) the rates of generation of non-metabolizable and metabolizable acids; (2) the rates of intestinal base absorption and of base delivery by dialysis; and (3) the influence of the ingestion of base-free tap water.

### MATERIALS AND METHODS

#### Subjects

The subjects comprised 18 anuric outpatients (11 females), age range 40–65 years, who had been undergoing post-dilutional haemodiafiltration thrice weekly for between 24 and 40 months. All subjects were in metabolic steady state, and consumed ad libitum diets lacking dairy products but supplemented with CaCO3 at between 20 and 60 mmol/day (mean 34 ± 11 mmol/day). The ionic composition and base content of the diets consumed at home by our patients were checked periodically as the raw weight of the various dietary components. From these records, our patients were shown to have rather constant alimentary habits. The majority were treated with antihypertensive drugs. No other medicine was administered, in particular sodium bicarbonate and/or active vitamin D products. The subjects did not suffer from any intestinal disturbance, and reported feeling fairly well.

The balance studies were carried out in the morning during the second dialysis session of the week. The patients did not ingest liquid or solid food during the dialysis session. The operational characteristics of haemodiafiltration are given in Table 1.

The research was completed before the establishment of a local ethics committee, but was carried out in accordance with the Declaration of Helsinki of the World Medical Association. Informed consent was obtained from each patient.

#### Study protocol

Blood was drawn anaerobically from the arterialized vein of the fistula at the beginning and 1 h after the end of haemodialysis. Plasma ultrafiltrate was collected anaerobically from the empty dialysis side of the filter at the same times. The tanks containing the concentrated solutions were weighed accurately before and at the end of each session in order to calculate, from the weight difference, the amounts of solutions delivered to the cartridge. The bags for intravenous infusion were also weighed to calculate the amounts of solution infused.
300 ml of oil, were used to collect the dialysis effluent, the amount of which was estimated from the weight difference. All weight measurements were carried out using the same bed scale, which was utilized by the patient during the dialysis (Weighing Bed, model V/D; Tassinari Bilance; Pieve di Cento, Bologna, Italy). The operational characteristics of the weighing bed were: capacity 150 kg; division 50 g; sensitivity 10 g. From each tank, 300 ml of dialysis effluent was withdrawn anaerobically. By means of a high-vacuum lyophilizer (Edwards; Minifast 470, series 1508), 250 ml was concentrated to 25 ml in order to increase the concentrations of total phosphorus (tP), SO\(_4^{2-}\), lactate, urate and blood urea nitrogen, so that they fell within the range compatible with reliable chemical measurements. The remaining 50 ml of effluent was utilized for all other measurements.

The mean dialysate inflow was 101 ± 7.8 litres. The haemodiafiltration solution was infused intravenously from 5-litre bags to give a total of 12 ± 0.47 litres per dialysis. The total solution (dialysate plus bag solution) delivered was 113 ± 8 litres. Finally, the total dialysate outflow was 115.65 ± 8.15 litres. The analytical ionic concentrations relevant to inflow, outflow and bag solutions are shown in the Appendix.

**Chemical analysis**

Sodium, potassium, calcium, magnesium, chloride, tP, sulphate, urate and blood urea nitrogen were measured in the plasma, plasma ultrafiltrate, inflow dialysate and outflow dialysate. In the plasma, inflow dialysate and outflow dialysate, pH, the partial pressure of CO\(_2\) (P\(\text{CO}_2\)) and total CO\(_2\) (t\(\text{CO}_2\)) were also measured. In the plasma ultrafiltrate only the measurement of t\(\text{CO}_2\) was carried out. Total protein and glucose only were measured in the plasma. The concentrations of total proteins, blood urea nitrogen, glucose, Na\(^+\), K\(^+\), total Ca\(^{2+}\) and Mg\(^{2+}\), Cl\(^-\), tP and urate were determined using an Hitachi 747 Autoanalyzer. Inorganic sulphate was determined by the turbidimetric method [11]. Lactate was measured by a specific enzymic method (Boehringer Mannheim). P\(\text{CO}_2\) and pH were measured with an ABL 505 gas analyser. t\(\text{CO}_2\) was measured using the ASTRA method [12]. All anions and cations are expressed as mmol·l\(^{-1}\), Ca\(^{2+}\) and Mg\(^{2+}\) as two times their molar concentrations, and tP as 1.8 times its molar concentration.

**Calculations**

The protein catabolic rate and the body fluid urea depuration index \([K_t\times V^{-1}\text{, where } K\text{ is dialysis clearance (l·min}^{-1}\text{), } t\text{ is duration of dialysis (min) and } V\text{ is the distribution volume (litres)}]\) were calculated from the standard equations of urea kinetic modelling in dialysis [13,14]. The depuration index refers to the number of occasions per unit of time that the distribution volume or its content of any filterable solute is subject to elimination through the dialysis cartridge.

In the plasma, plasma ultrafiltrate and dialysis solutions, the actual bicarbonate concentration (HCO\(_3^-\)) was calculated as follows:

\[
\text{HCO}_3^- (\text{mmol·l}^{-1}) = t\text{CO}_2 - P\text{CO}_2 \times \alpha \tag{1}
\]

at actual pH, where \(\alpha\) is the solubility coefficient of CO\(_2\) [15] (approx. 0.0301). The value of P\(\text{CO}_2\) in the plasma ultrafiltrate was considered equal to the plasma P\(\text{CO}_2\), in view of the equal distribution of CO\(_2\) between the intravascular and interstitial fluids [15].

The pH was calculated from the Henderson–Hasselbalch equation. Titratable acidity (TA) and titratable basicity (TB) in dialysis fluids were calculated from the molar concentration of t\(\text{CO}_2\), assuming \(pK_t = 6.8\), and the molar concentration of t\(\text{CO}_2\) assuming \(pK'_t = 6.1\), at the reference and the actual pH of the dialysate. The contribution of creatinine was disregarded due to the low \(pK'_t\) of this substance when compared with the actual pH of the alkaline dialysate effluent. In the plasma, base excess (BE) was calculated according to Siggaard-Andersen [16]. The excess of non-metabolizable inorganic cations \([\text{C}_{\text{in}}^-\text{mmol}] = \text{Na}^+ + \text{K}^+ + 2\text{Ca}^{2+} + 2\text{Mg}^{2+}\)] over non-metabolizable inorganic anions \([\text{A}_{\text{in}}^-\text{mmol}] = \text{Cl}^- + 1.8\text{tP} + 2\text{SO}_4^{2-}\)] measures the amount of total base (NB), i.e. the sum of bicarbonate (HCO\(_3^-\)) plus metabolizable anions (A\(_{\text{in}}^-\)) at pH 7.40 [17–20], according to the following equations:

\[
\text{NB (mmol·l}^{-1}) = \text{C}_{\text{in}}^- - \text{A}_{\text{in}}^- \\
= \text{A}_{\text{in}}^- + \text{HCO}_3^- - \text{TA} \tag{2}
\]

on titration to pH 7.40. In the case of plasma, TA or TB is replaced by BE\(_s\), as follows:

\[
\text{NB (mmol·l}^{-1}) = \text{A}_{\text{in}}^- + 23.85 + \text{BE} \tag{2a}
\]

on titration to pH 7.40, where 23.85 represents the bicarbonate concentration at pH 7.40 and P\(\text{CO}_2 = \text{40 mmHg (5.33 kPa)}\) [19,20]. Eqns (2) and (2a) were obtained as illustrated in the Appendix.

The amounts of organic anions (A\(_{\text{inf}}^-\) or R·COO\(^-\)) in dialysis fluids and plasma were derived from equations (2) and (2a) respectively. For the plasma ultrafiltrate and inflow dialysate, the concentrations of organic anions (A\(_{\text{in}}^-\)) were derived from eqn (2), disregarding the negligible amounts of TA or TB [21]. Equations (2) and (2a) are in accordance not only with the law of electroneutrality, but also with the operational principle of titration [20].

The anion gap (AG) in the plasma was calculated as follows [22]:

\[
\text{AG (mmol·l}^{-1}) = \text{Na}^+ - \text{Cl}^- - t\text{CO}_2 \tag{3}
\]

To perform dialysis balances, the inflow, outflow and
average ionic concentrations of dialysis fluids were obtained as illustrated in the Appendix.

Assuming a whole-body balance of water and non-metabolizable (inorganic) cations and anions of zero, the intestinal absorption of NB in our anuric patients can be derived from the following equations:

\[
\text{Dialysis delivery} + \text{intestinal absorption} = \text{dialysis elimination} \tag{4}
\]

and

\[
\text{Intestinal absorption} = \text{dialysis elimination} - \text{dialysis delivery} \tag{4a}
\]

When eqn (4a) was applied to the various inorganic cations and anions of the dialysis solutions, the intestinal absorption of NB was calculated from the algebraic sum of the following dialysis balances (Bal.):

\[
\begin{align*}
\text{NB(A) (mmol)} & = \text{Na}^+ (\text{Bal.}) + \text{K}^+ (\text{Bal.}) + 2\text{Ca}^{2+} (\text{Bal.}) \\
& + 2\text{Mg}^{2+} (\text{Bal.}) - \text{Cl}^- (\text{Bal.}) - 1.8t\text{P} (\text{Bal.}) \\
& \tag{5}
\end{align*}
\]

on titration to pH 7.40, where NB(A) is the intestinal absorption of bicarbonate and metabolizable anions [23].

Whereas in dialysis electrolyte balances all the ions present in the inlet and outlet dialysate solutions must be measured, as far as the intestinal absorption of NB is concerned (according to eqn 5), the elimination of SO\(_4^{2-}\) can be disregarded, since its generation takes place from neutral sulphur oxidation of sulphur-containing amino acids after their intestinal absorption [19,23].

The extracellular volume of dry body weight (BW) (\(V_d\), in litres) was calculated from the following equation, the derivation of which is illustrated in the Appendix:

\[
V_d (\text{litres}) = \frac{[2\text{SO}_4^{2-}\text{elimination} - \Delta\text{BW} \times (2\text{SO}_4^{2-}\text{pre})]}{[(2\text{SO}_4^{2-}\text{pre}) - (2\text{SO}_4^{2-}\text{post})]} \tag{6}
\]

where \(\Delta\text{BW}\) indicates the interdialytic expansion of \(V_d\), while '2\text{SO}_4^{2-}\text{pre}' and '2\text{SO}_4^{2-}\text{post}' are the extracellular pre- and post-dialysis concentrations respectively of SO\(_4^{2-}\) (mmol·l\(^{-1}\)). The intradialytic distribution space of actual bicarbonate was calculated by means of eqn (6), by substituting HCO\(_3^-\) gain for 2SO\(_4^{2-}\) loss.

The extracellular pool of NB, calculated both before and after dialysis, was obtained from pre- and post-dialysis extracellular volumes respectively multiplied by the corresponding extracellular NB concentrations.

**Statistical analysis**

Values are reported as means ± S.D. One- and two-way ANOVA, Student’s \(t\) tests for paired and unpaired data, and simple and multiple linear regression analysis were performed (STATISTICA 5.5; http://www.statsoft.com).

**RESULTS**

The most important characteristics of post-dilutional haemodiafiltration are given in Table 1. Of interest is the fact that \(Kt · V^{-1}\) was significantly higher than the normalized protein catabolic rate \([t(17) = 2.88; P = 0.01]\).

Table 2 shows that the sum of cation concentrations measured before dialysis was not different from that measured after dialysis. In contrast, the sum of anions was decreased significantly by dialysis, due to high phosphate and sulphate clearances. As a consequence, the inorganic cation–anion difference (C\(_{\text{in}}\)–A\(_{\text{nm}}\); i.e. NB) increased, along with HCO\(_3^-\), BE and pH, from the beginning to the end of dialysis. It should be stressed that both AG and organic anion concentrations were normal, without any significant dialysis-induced variations.

Finally, at the end of dialysis, the bicarbonate gradient between the inflow dialysate and the plasma ultrafiltrate had almost completely disappeared.

Table 3 shows that the dialysis balances of the sums of inorganic cations and anions were significantly negative. It is noteworthy that the sum of the cation balance was not different from that of the anion balance \([t(17) = 0.87; P = 0.40]\). As a consequence, the cation–anion difference balance, i.e. the balance of NB (−6.86 mmol), is not different from zero. There is, however, a positive balance of NB, as lactate plus bicarbonate amounts to approx. 500 mmol per treatment \((273 + 244 = 517\) mmol). Therefore equivalent quantities of NB as non-lactate and non-acetate anions must be lost to obtain overall NB balances not different from zero. This indicates that, during dialysis, a continuous generation of metabolizable acids occurs; after consumption of bicarbonate, these are eliminated as organic anions. This explains why the apparent distribution volume of bicarbonate, delivered during dialysis, was as high as 93% of dry BW, a value much greater than that \((51\%\) of dry BW) measured by Uribarri et al. [4] before dialysis, by means of bicarbonate infusion. Finally, since TA is contributed to by the high Pco\(_2\) (69 mmHg; 9.2 kPa) of the inlet dialysate, its positive balance (97.8 mmol) is completely eliminated by the lungs.

Figure 1 shows that the rate of intestinal NB absorption and the rate of sulphuric acid generation were 66 ± 26 and 59 ± 21 mmol/2 days respectively, i.e. not significantly different \([t(17) = 0.87; P = 0.40]\).

The plasma NB concentration measured before dialysis was 42.50 ± 4.3 mmol·l\(^{-1}\), which, when corrected for the concentration/dilution ratio of total plasma proteins (adjusted NB), was not different from that measured after
Acid–base balance in haemodialysis

Table 2 Acid–base data for 18 dialysis patients

Values are means ± S.D. Significance of differences: *P < 0.05, **P < 0.01, ***P < 0.001 for after dialysis compared with before dialysis; †P < 0.05, †††P < 0.001 for dialysate inflow compared with ultrafiltrate.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Plasma</th>
<th>Ultrafiltrate</th>
<th>Dialysate inflow</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
<td>After</td>
<td>Before</td>
</tr>
<tr>
<td>Tonicity (mOsm·l⁻¹⁻)</td>
<td>284 ± 5</td>
<td>285 ± 7.6</td>
<td>291 ± 6.47</td>
</tr>
<tr>
<td>Sum of C⁺⁺⁺ (mmol·l⁻¹⁻)</td>
<td>152.3 ± 3.5</td>
<td>150.6 ± 2.5</td>
<td>150.6 ± 2.4</td>
</tr>
<tr>
<td>Sum of A⁻⁻⁻ (mmol·l⁻¹⁻)</td>
<td>109.8 ± 4.9</td>
<td>103.3 ± 3.4***</td>
<td>120 ± 2.8</td>
</tr>
<tr>
<td>NB (mmol·l⁻¹⁻)</td>
<td>42.5 ± 4.3</td>
<td>47.35 ± 4.4***</td>
<td>32 ± 3.0</td>
</tr>
<tr>
<td>HCO₃⁻ (mmol·l⁻¹⁻)</td>
<td>20.44 ± 2.9</td>
<td>24.6 ± 2.1***</td>
<td>23 ± 3.2</td>
</tr>
<tr>
<td>A⁻ (mmol·l⁻¹⁻)</td>
<td>22.57 ± 4.2</td>
<td>22.48 ± 4.9</td>
<td>9 ± 2.5</td>
</tr>
<tr>
<td>BE (mmol·l⁻¹⁻)</td>
<td>-3.9 ± 3.0</td>
<td>1.0 ± 2.2***</td>
<td>-</td>
</tr>
<tr>
<td>AG (mmol·l⁻¹⁻)</td>
<td>14.74 ± 3.84</td>
<td>12.74 ± 4.33</td>
<td>-</td>
</tr>
<tr>
<td>PCO₂ (mmHg)</td>
<td>40 ± 4.8</td>
<td>38 ± 3.6*</td>
<td>40 ± 4.8</td>
</tr>
<tr>
<td>pH</td>
<td>7.33 ± 0.04</td>
<td>7.43 ± 0.04***</td>
<td>7.38 ± 0.04</td>
</tr>
</tbody>
</table>

Table 3 Electrolyte and acid–base balances for a 2-day interdialytic period in 18 dialysis patients

Values are means ± S.D. t, Student's t test.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Total (mmol)</th>
<th>Input</th>
<th>Output</th>
<th>Balance</th>
<th>t</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sum of C⁺⁺⁺</td>
<td>16572 ± 1154</td>
<td>17114±1164</td>
<td>-542 ±222</td>
<td>10</td>
<td>&lt; 0.0001</td>
<td></td>
</tr>
<tr>
<td>Sum of A⁻⁻⁻</td>
<td>12392 ± 902</td>
<td>12926±926</td>
<td>-535 ±213</td>
<td>10</td>
<td>&lt; 0.0001</td>
<td></td>
</tr>
<tr>
<td>NB</td>
<td>4180 ± 325</td>
<td>4187±229</td>
<td>-6.86 ±26</td>
<td>0.87</td>
<td>0.40</td>
<td></td>
</tr>
<tr>
<td>HCO₃⁻</td>
<td>-3511 ± 271</td>
<td>3168±290</td>
<td>342 ±160</td>
<td>9.06</td>
<td>&lt; 0.0001</td>
<td></td>
</tr>
<tr>
<td>A⁻</td>
<td>728 ± 228</td>
<td>980±235</td>
<td>-251 ±159</td>
<td>6.7</td>
<td>&lt; 0.0001</td>
<td></td>
</tr>
<tr>
<td>Lactate</td>
<td>416 ± 21</td>
<td>143±41</td>
<td>273 ±52</td>
<td>19</td>
<td>&lt; 0.0001</td>
<td></td>
</tr>
<tr>
<td>TA</td>
<td>59 ± 23</td>
<td>-38.9±43</td>
<td>97.8 ±34</td>
<td>12</td>
<td>&lt; 0.0001</td>
<td></td>
</tr>
</tbody>
</table>

Figure 1 Rates of intestinal NB absorption and acid generation over a 2-day interdialytic period in 18 dialysis patients

It is shown that the intestinal absorption of NB does not differ from 2 × the molar production of H₂SO₄.

dialysis [adjusted NB, 48.3 ± 6 mmol·l⁻¹⁻; NB measured after dialysis, 47.3 ± 4.4 mmol·l⁻¹⁻; t(17) = 1.065; P = 0.302] (Figure 2).

Figure 2 Plasma concentrations of NB in 18 dialysis patients

The concentration of NB measured before dialysis (left panel) was lower than the pre-dialysis concentration of NB adjusted to dry BW (middle panel); the latter was not different from the concentration of NB measured after dialysis (right panel).

The concentration of total plasma proteins was 69.9 ± 3 g·l⁻¹ before and 72.6 ± 6.2 g·l⁻¹ after dialysis. Finally, the Vₐ values of SO₄⁻² were 18.54 ± 5.66 litres before and 15.88 ± 5.60 litres after dialysis. We also found...
that the extracellular pools of NB measured before and after dialysis were not different from each other [before, 589 ± 195 mmol; after, 567 ± 183 mmol; \( t(17) = 1.89; P > 0.05 \)]. The average amount of kitchen salt ingested by our patients was 11 ± 3 g/day.

**DISCUSSION**

**Methodological considerations**

Balance studies in haemodialysis patients present technical problems due to the large volumes of dialysis solutions that are routinely used. Thus we not only applied the methodological precautions relevant to the measurement of the various electrolytes and acid–base parameters, but analysed statistically the homogeneity and normality of the variance. We observed that the mean values of all the inlet and outlet electrolyte and acid–base pairs were characterized by homogeneity of variance. The normality of the variance was rarely found to be skewed, and any skewing was not serious, such that the application of parametric and non-parametric tests did not give different results. Moreover, with the application of the randomized block design of ANOVA for the reduction of experimental error, we demonstrated that the wide deviations in values for plasma, plasma ultrafiltrate and (particularly) dialysis balances were not due to methodological inaccuracies, but rather to inter-individual variability within our dialysis population. For example, we found unexplained percentages of total variance as low as 0.3% for sodium balances and 1.5% for chloride balances. Certainly, these residual variance percentages included measurement errors, together with other unknown dispersion factors. The accuracy of the data obtained was due to the use of the lyophilizer, which permitted concentration of all dilute fluids. This increased the accuracy of our measurements. This, together with the stable metabolic condition of our patients, justified the performance of the study during a single dialysis session.

When balance studies are performed it is essential that the same objective measurement be applied to the evaluation of input, output and composition of body fluids [20]. Our present study of the dialysis base balance and acid–base status of our patients is based on this assumption, while also complying with the law of electroneutrality and the operational principles of titration (see eqn 2) [20].

**Acid accumulation in dialysis patients**

**Loss of metabolizable anions**

At the end of the interdialytic period, our patients presented with typical non-carbonic acidosis (Table 2). According to the literature, such acid accumulation is attributable to the endogenous accumulation of sulphuric acid and non-metabolizable organic acids in excess of intestinal base absorption, and to metabolizable acids, whose conjugate anions are lost as salts of inorganic cations [24]. However, the conjugate anions of metabolizable acids are not lost during the interdialytic period in anuric dialysed patients, and thus H⁺ ions are not produced from this source, as first observed by Gennari [8]. Thus the amount of endogenous acid generated in anuric patients is reduced by approximately one half as compared with the amount calculated using the formula of Gotch et al. [25] in the same subjects.

**Production of non-metabolizable organic acids**

An important source of endogenous acids is thought to be the production of non-metabolizable organic acids, such as uric acid, hippuric acid and oxalic acid. Since all of these substances are neither metabolizable nor eliminated by the kidney in anuric subjects, they would be expected to accumulate in the body fluids, increasing the AG beyond the normal upper limit of 16 mmol·l⁻¹ [22]. In fact the opposite occurred; the pre-dialysis AG was only 14.7 mmol·l⁻¹ in our patients (see Table 2) and 12 mmol·l⁻¹ in those of Uribarri [4]. The normal values of AG observed in our dialysis population were confirmed by the normal concentrations of organic anions (A⁻m) in the same individuals, with no difference between pre- and post-dialysis levels (see Table 2).

To explain this AG behaviour in uremic patients, it has been suggested that, in end-stage renal failure, the production rates of non-metabolizable organic anions may be diminished and that adaptive changes in intestinal (mainly colonic) secretion may account for ongoing balance between their production and elimination rates. If colonic secretion of these acids were associated with countertransport of HCO₃⁻ or bicarbonate precursors, their acidic effect would be neutralized completely [26]. In conclusion, in our patients no contribution to pre-dialysis acidosis could be demonstrated from the accumulation of non-metabolizable organic acids.

**Sulphuric acid production**

In uraemic dialysed subjects, sulphuric acid production has generally been found to be ~40% lower than in normal subjects; this has been observed in patients undergoing CAPD [5,6] or extracorporeal dialysis [10]. In the present study, however, the elimination of SO₄²⁻ by dialysis (Figure 1) was higher than that found previously [5,6,10] and similar to that measured in normal subjects on the similar mixed protein intakes [27].

**Intestinal base absorption**

In the steady state, inorganic cations and anions absorbed by the intestine are eliminated by the kidney and/or by dialysis. This has clearly been demonstrated by Oh [3], who found close correlations between the intestinal absorption of both inorganic cations and anions and their
renal excretion. These absorption and excretion data were measured in subjects with normal and reduced renal function, in balance studies applied to diets and faeces, in both steady-state and non-steady-state metabolic conditions [3]. The indirect approach to intestinal base absorption is now widely accepted in the literature [3,17,18,26,28,29], and has proved satisfactory in peritoneal dialysis studies performed by us and others [5,6]. The average NB content of our patients’ home diet was approx. 80±30 mmol/day if supplemented with CaCO$_3$, i.e. quite similar to that of normal subjects [30] and more than adequate to account for the rate of intestinal absorption (Figure 1). As a consequence, it is highly improbable that, under these conditions, net acid accumulation will have taken place in our patients.

**Base contribution by dialysis to acid–base correction**

According to the literature, the object of dialysis is to restore the body’s burden of bases through positive base balances [8,31]. However, while bicarbonate delivery and elimination are measured correctly [8,25], the chemical measurements of organic anions that have been utilized so far have restricted loss to only a few types. Thus the chemical approach gives rise necessarily to organic anion balances that are less negative (or more positive) than they actually are [25,31]. The negative balances of non-lactate (non-acetate) organic anions (~500 mmol per treatment; Table 3) in bicarbonate dialysis indicate that an equivalent intradialytic generation of organic acids takes place, H$^+$ ion release from which gives rise to ongoing consumption of dialysis-delivered bicarbonate. This explains why such large bicarbonate distribution volumes are found in these patients (93% of BW), as suggested by Gennari [32].

In spite of the ongoing extracellular bicarbonate consumption, equilibrium conditions were attained in our patients; post-dialysis extracellular base concentrations were quite similar to, but never greater than, concentrations in the inflow dialysate (28 and 31 mmol·l$^{-1}$ respectively; Table 2). However, cases have been reported [32] in which plasma tCO$_2$ increased less than expected and, in isolated cases, actually fell during dialysis; this was described as ‘a change that can only be explained by a dramatic and sustained rise in organic acid production during the treatment’ [32]. In conclusion, the correction of acid–base parameters occurred in our patients, in spite of no donation of NB by dialysis.

**Contribution to acidosis of body fluid expansion**

In spite of virtually no net acid production (endogenous generation minus intestinal base absorption) (Figure 1), our patients developed a non-carbolic, so-called ‘metabolic’, acidosis [8]. It is, therefore, necessary to suggest alternative hypotheses to explain the observed pre-dialysis acidosis in uraemic patients. The most likely hypothesis is that dilution acidosis develops as a consequence of ingestion of tap water. In fact, normal tonicity of body fluids in uraemic patients is preserved by water ingestion, in spite of the dietary-related accumulation of impermeant solutes. However, water ingestion, which prevents the plasma tonicity from increasing, at the same time dilutes extracellular NB concentrations (Table 2, Figure 2). It is worth stressing that the NB concentration in tap water is 36 mmol·l$^{-1}$ lower than that in the extracellular fluids (Table 2) [33].

As pointed out above, in patients on either haemodialysis or CAPD, the balances of NB and the net production of endogenous acid do not differ from zero [4–6]. Thus the only major difference between haemodialysis and CAPD is that the intermittent haemodialysis is characterized by water retention, extracellular volume expansion and pre-dialysis acidosis, while CAPD is characterized by ongoing water elimination, no intermittent expansion of the extracellular space and normal extracellular base concentrations. It is therefore very likely that, in haemodialysis, it is the interdialytic water retention that leads to pre-dialysis acidosis.

In fact, when intensive (i.e. daily) dialysis treatments are carried out, both water ingestion and extracellular fluid expansion are prevented, along with pre-dialysis acidosis, with plasma bicarbonate approaching the levels observed in patients on CAPD. Moreover, when bicarbonate was administered to haemodialysis patients [34] as sodium bicarbonate in order to mitigate pre-dialysis acidosis, pre-dialysis HCO$_3^-$ increased less than expected, while a greater than usual interdialytic increase in body weight was observed, evidently as a consequence of the excess of sodium and water ingestion, which again led to dilution acidosis.

Finally, it has been demonstrated that dilutional acidosis is, at least in part, compensated for by an ongoing shift of base from the intracellular and bone buffer systems to the extracellular volume [35]. This process would be expected, therefore, to have increased the pre-dialysis extracellular NB content in our patients, thus making the fall in NB concentration less severe. In contrast, in our patients: (1) the extracellular pools of NB measured before and after dialysis were not different, and (2) the pre-dialysis NB concentrations, when adjusted to dry BW, achieved values not different from those actually measured after the end of dialysis (Figure 2). These observations tend to exclude the participation of intracellular and bone buffer systems in moderating dilution acidosis. In this regard, even though the complex relationships between bone metabolism and uraemic acidosis are beyond the scope of this paper, we think it improbable that reversible dilution acidosis may induce unrelenting acid accumulation, leading to the depletion of bone buffer systems and osteomalacia. The reason why the intracellular buffer capacity does not intervene to
oppose dilution acidosis in our haemodialysis patients cannot be explained by the present data.

Conclusions
Our present study has led to the following conclusions. (1) During the interdialytic period, the uremic patient generates endogenous non-metabolizable acids (mainly sulphuric acid) at a rate quite similar to that of intestinal NB absorption. This leads to a reciprocal and complete acid–base neutralization. (2) The interdialytic ingestion of free tap water, induced by the diet-related accumulation of impermeant solutes, brings about an isotonic fluid expansion, which leads to dilution acidosis. (3) During dialysis treatment, the isotonic elimination of water and impermeant solutes (mainly NaCl) restores the extracellular volume to normal values, while keeping the extracellular NB burden constant. Thus the postdialysis increase in NB concentration seems to be caused mainly by processes of extracellular volume contraction. (4) From a practical point of view, our results suggest that normoproteic diets should be adopted which lack dairy products, are supplemented with alkaline calcium salts and contain substantial amounts of fruit and vegetables.

Reduced NaCl ingestion (approx. 5 g day) observed for our patients) is also mandatory to prevent profound pre-dialysis acidosis stemming from extracellular water overload.

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APPENDIX

Ionic compositions
The ionic composition of the inflow dialysate was as follows (mmol·l⁻¹): Na⁺ 140 ± 1.23; K⁺ 2.23 ± 0.48; 2Ca²⁺ 3.56 ± 0.13; 2Mg²⁺ 1.07 ± 0.06; Cl⁻ 109.7 ± 1.58; NB 37.6 ± 2.0; tCO₂ 33.12 ± 0.94; acetate 6.59 ± 2.5; TA 0.58 ± 0.2. In addition, PCO₂ = 69 ± 7.2 mmHg (9.2 ± 0.96 kPa) and pH = 7.27 ± 0.04 (values are means ± S.D.).

The ionic composition relevant to bag solutions was (mmol·l⁻¹): Na⁺ 140 ± 0.65; K⁺ 0.83 ± 0.62; 2Ca²⁺ 3.14 ± 0.20; 2Mg²⁺ 1.08 ± 0.7; Cl⁻ 113 ± 3.26; lactate 34.3 ± 0.44.

The ionic composition relevant to outflow dialysate was (mmol·l⁻¹): Na⁺ 140 ± 0.65; K⁺ 2.79 ± 0.42; 2Ca²⁺ 3.46 ± 0.17; 2Mg²⁺ 1.90 ± 0.07; Cl⁻ 111 ± 2.12; 1.8tP 0.31 ± 0.11; 2SO₄²⁻ 0.51 ± 0.18; NB 36.22 ± 1.85; A⁻ 8.56 ± 2.396; tCO₂ 28.70 ± 1.0; lactate 1.25 ± 0.46; urate 0.043 ± 0.011; TA – 0.336 ± 0.37. In addition, PCO₂ = 42 ± 3.76 mmHg (5.6 ± 0.5 kPa) and pH = 7.438 ± 0.031.

Miscellaneous equations

Inflow dialysate volume (litres per dialysis treatment) = outflow dialysate volume − ABW – bag infusion volume

Inflow dialysate electrolyte concentration (mmol·l⁻¹) = total electrolyte amount from tank / total inflow dialysate volume

Total outflow electrolyte amount (mmol per dialysis treatment) = total outflow volume × outflow dialysate concentration

Derivation of eqn (2)
First:

\[ TA + Na^+ + K^+ + 2Ca^{2+} + 2Mg^{2+} + NH_4^+ = Cl^- + 1.8tP + 2SO_4^{2-} + A^- + HCO_3^- \ (mmol) \]

according to the law of electroneutrality and the principle of titration to pH 7.40. By rearranging:

\[ [Na^+ + K^+ + 2Ca^{2+} + 2Mg^{2+} + NH_4^+] - [Cl^- + 1.8tP + 2SO_4^{2-}] = A^- + HCO_3^- - TA \]

at pH 7.40, from which:

\[ NB = A^- + HCO_3^- - TA \]

on titration to pH 7.40. NH₄⁺ is disregarded when plasma, plasma ultrafiltrate and dialysis solutions are considered.

Derivation of eqn (6)
First:

\[ (V_d \text{ post}) \times (2SO_4^{2-} \text{ post}) + (2SO_4^{2-} \text{ elimination}) = (V_d \text{ pre}) \times (2SO_4^{2-} \text{ pre}) \]

and

\[ V_d \text{ post (litres)} = (V_d \text{ pre}) - ABW \]

where ‘post’ and ‘pre’ denote before and after dialysis respectively. Therefore:

\[ (V_d \text{ post}) \times (2SO_4^{2-} \text{ post}) + (2SO_4^{2-} \text{ elimination}) = (V_d \text{ post}) \times (2SO_4^{2-} \text{ pre}) + ABW \times (2SO_4^{2-} \text{ pre}) \]

By rearranging:

\[ V_d \text{ post (litres)} = \frac{[(2SO_4^{2-} \text{ elimination}) - ABW \times (2SO_4^{2-} \text{ pre})]}{(2SO_4^{2-} \text{ pre}) - (2SO_4^{2-} \text{ post})} \]
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