Spurious estimations of sodium removal during CAPD when \([\text{Na}]^+\) is measured by Na electrode methodology

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Spurious estimations of sodium removal during CAPD when \([\text{Na}]^+\) is measured by Na electrode methodology.

Background. The aim of this study was to investigate the effect of pH and glucose concentration on sodium removal and the dialysate and plasma sodium ratio \((D/\text{PNa})\) as measured by means of a flame photometer (NaF) or direct ion-selective electrode (NaE) in continuous ambulatory peritoneal dialysis (CAPD).

Methods. In vitro, glucose concentration, pH, NaF, and NaE were measured in fresh peritoneal dialysis solutions (PDSs) before and after the addition of glucose or KOH. In vivo, 66 four-hour peritoneal equilibration tests were performed in 35 patients on CAPD using a low pH PDS with a glucose concentration of 3.86%.

Results. In vitro, NaF and NaE were significantly influenced by the glucose concentration and pH of the PDS. In vivo, in fresh PDS, there was a significant difference between the NaF and NaE results; the respective median values were 132.1 (interquartile range 129.3 to 137.5) versus 138.0 (134.4 to 141.5) mmol/L \((P < 0.0001)\). The D/\text{PNa} ratio calculated by NaE was significantly lower than that calculated by NaF \((0.88 \pm 0.03, P < 0.0001)\), whereas there was no significant difference between the NaE and NaF values after correction for plasma water and a Donnan factor of 0.96. Sodium removal was significantly lower when calculated as NaE than when calculated as NaF \((43.9 \pm 32.7, P < 0.0001)\).

Conclusions. The fresh PDS sodium concentration can be corrected using a glucose concentration-related factor. The D/\text{PNa} ratio calculated as NaE is not different after correction for plasma water and a Donnan factor of 0.96. Sodium removal must be measured by means of NaF rather than NaE. This could have an important clinical impact.

The concentration of sodium in biological fluids is usually measured by means of a flame photometer (F) and/or a direct ion-selective electrode (E) [1]. In plasma, the sodium measured by F accounts for the total sodium concentration \((\text{NaF}_p)\), but for dialytic purposes, it is actually more interesting to know the total sodium concentration in plasma water \((\text{NaF}_{pw})\), which can be calculated by means of an equation that corrects NaFp for the volume occupied by plasma proteins and plasma lipids [2]. \(\text{NaF}_{pw}\) is generally 9 mmol/L higher than NaFp. In plasma water, a certain amount of the total sodium \((\sim 7 \text{ mmol/L})\) is complexed with anions (particularly proteins and bicarbonate) and is therefore ionically inactive and cannot diffuse. The ionically active concentration of sodium in plasma water \((\text{NaE}_{pw})\) can be directly measured by E and is approximately 7 mmol/L lower than \(\text{NaF}_{pw}\) and 2 mmol/L higher than \(\text{NaF}_p\).

In hemodialysis, the sodium concentration in the dialysate fluid \((\text{NaF}_d)\) measured by F accounts for the total sodium; the number does not need any correction because, unlike plasma, dialysate fluids are protein free. However, as in plasma water, a fraction of the total sodium is partially complexed with various anions (mainly bicarbonate and acetate). As this amount is approximately 4 mmol/L at usual bicarbonate and acetate concentrations, the ionized sodium concentration in the dialysate \((\text{NaE}_d)\) measured by direct E is 4 mmol/L lower than \(\text{NaF}_d\) [3].

Sodium measured in plasma water by the ion-selective electrode \((\text{NaE}_{pw})\) corrected for a Donnan factor of 0.96 can be considered as the amount of diffusible sodium, as can the \(\text{NaE}_d\) measured in protein-free dialysate [4].

Thus, F measures the sodium concentration and direct E measures the sodium activity in the solution [5, 6]. Only the active sodium (ionized sodium) is able to move across cell and dialysis membranes by diffusion. The difference between the activity of sodium in the blood and in the dialysate is the driving force for diffusion across membranes [7].

Raising the pH of the solution or adding other ions (carbonate, bicarbonate, phosphate) effectively lowers
the number of noncomplexed sodium ions in solution and reduces the activity of sodium [5].

In peritoneal dialysis, sodium sieving can be demonstrated by the decrease in the dialysate sodium concentration during the initial phase of a dialysis dwell, especially with a glucose concentration of 3.86% [8–10]. The sodium concentration ratio between the dialysate and plasma (D/PNa) is an indirect measure of (aquaporin-mediated) transcellular water transport [11–16].

Sodium removal during peritoneal dialysis closely correlates with net fluid removal [12, 17–19]. Increased peritoneal permeability is associated with a decrease in fluid and sodium removal [20], and this could partially contribute to the high cardiovascular mortality rate observed in these patients [21].

Sodium transport across the peritoneal membrane is extremely complex and is still not fully understood [11]. However, in animal and clinical studies, sodium concentration has been indifferently assessed by F, by direct E, or by indirect E [9, 12–19, 22, 23].

The most commonly used PD solutions contain high concentrations (1.36 to 3.86%) of glucose and low pH (5.0 to 5.5). The high glucose concentration and low pH of PD solutions may affect other solutes and measurement methods (for example, the determination of creatinine levels) [24, 25].

The aim of this study was to verify whether the concentration of sodium in such PD solutions is different when measured by F or direct E.

**METHODS**

**Patients**

Sixty-six peritoneal equilibration tests (PET) were performed in 35 continuous ambulatory peritoneal dialysis (CAPD) patients (14 males and 21 females). Most of the patients had more than one evaluation (2 evaluations in 8, 3 evaluations in 10, and 4 evaluations in 1), with an interval of at least six months between one evaluation and another. All of the patients had been on regular CAPD treatment for at least three months before the first PET, and their medical condition was stable; all had been peritonitis free for at least one month.

The underlying renal diseases were chronic glomerulonephritis (N = 13), adult polycystic kidney disease (N = 7), interstitial nephritis (N = 7), hypertensive nephrosclerosis (N = 4), diabetic nephropathy (N = 2), and unknown (N = 2). At the time of the last evaluation, the mean age of the patients was 59.7 years (range 29 to 85). The mean time on CAPD was 30 months (range 3 to 103), and the median residual urine production was 807 mL/24 hours (range 0 to 3800). Eight of the patients were anuric.

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**Study protocol**

*In vitro study.* The glucose concentration, total sodium (by F), ionized sodium (by direct E), and pH of fresh PD solutions were measured twice, and the measurements were repeated after adding glucose (using two PD solutions containing 1.36% anhydrous glucose and a 132 and 136 mmol/L nominal sodium concentration, respectively) or KOH (using one PD solution containing 3.86% anhydrous glucose and a 136 mmol/L nominal sodium concentration) in order to neutralize the acidic pH.

*In vivo study.* The PETs were performed as part of the patients’ routine clinical evaluation, but differed from the classic method [25] insofar as two different PD solutions containing anhydrous glucose 3.86% were used (solution A in 34 and solution B in 32 PETs). The nominal compositions of the two solutions are shown in Table 1. In all the cases, the dwell prior to the PET (overnight dwell) was performed using a PD solution containing a glucose concentration of 1.36% with lactate as the buffer; the overnight dialysate was instilled at about 11 p.m. in the evening before the test and was drained at about 7 a.m.

Blood samples were drawn at the start of the tests, and fresh PD fluid (D0) samples were taken from the bag at the end of the infusion. After the complete infusion of the PD solution, 20 mL dialysate samples were taken at 1, 60, 120, and 240 minutes (D1', D60', D120', D240) after 30 mL of dialysate had been flushed back. The patients were instructed to sit up or move about in bed before the drawing of each dialysate sample; otherwise, they remained recumbent during the four-hour investigation.

After 240 minutes, the dialysate was collected by gravity for at least 20 minutes. The volume of the infused fresh PD solution and the drained dialysate were measured by weighing the bag and then subtracting the weight of the empty bag; no corrections were made for the differences in the specific weight of the solutions.

**Analytical methods**

The whole plasma and dialysate urea, creatinine, total protein, and glucose concentrations were analyzed using

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**Table 1.** Nominal composition of the two peritoneal dialysis solutions

<table>
<thead>
<tr>
<th></th>
<th>Solution A</th>
<th>Solution B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose g/dL</td>
<td>3.86</td>
<td>3.86</td>
</tr>
<tr>
<td>Lactate mEq/L</td>
<td>40</td>
<td>37.5</td>
</tr>
<tr>
<td>Na mEq/L</td>
<td>132</td>
<td>136</td>
</tr>
<tr>
<td>Ca mEq/L</td>
<td>95</td>
<td>102.7</td>
</tr>
<tr>
<td>Mg mEq/L</td>
<td>3.5</td>
<td>3.5</td>
</tr>
<tr>
<td>Osmolality mOsm/L</td>
<td>483</td>
<td>492.4</td>
</tr>
<tr>
<td>pH</td>
<td>5.0–6.5</td>
<td>5.0–6.5</td>
</tr>
</tbody>
</table>
a Hitachi 717 (Tokyo, Japan), with the creatinine concentrations being corrected by means of a dilutional method to eliminate the effect of the high dialysate glucose concentration. The total dialysate and plasma sodium concentrations were analyzed twice using an IL 943 flame photometer (Instrumentation Laboratory, Milan, Italy). The concentration of ionized sodium in the dialysate and blood was analyzed using a direct ion-selective electrode (Nova 1, Nova Biomedical Corp., Waltham, MA, USA). The same concentrations were determined in the PD dialysate of overnight dwell before the PET.

The pH in the dialysate was measured using a State Profile 4 (Nova).

Calculations

The aqueous concentrations of the solutes in plasma water \(C_{pw}\) were calculated from their measured whole plasma concentrations \([\text{plasma concentration} (C_{pc})]\) corrected for plasma lipid and total protein concentrations according to the following equation [2]:

\[
C_{pw} = u \cdot C_{pc}
\]

where \(u = 1/(1 - V_{lip} - 0.000718 \cdot C_{prot})\). \(C_{prot}\) is the total plasma protein concentration in g/L, and \(V_{lip}\) is the fractional volume of plasma lipids (in this study, a normal value of 0.016 was used). This correction was obviously not used in the case of the sodium concentrations measured by direct E \((Na_{Ed})\).

No correction for dialysate protein concentration was made because of the low concentration of proteins in the dialysate (0.063 ± 0.022 g/dL after 240 minutes).

Sodium removal \((NaR)\) was calculated as follows:

\[
NaR = V \cdot Na_{Out} - V \cdot Na_{In}
\]

where \(V\) is the volume of the PD solution in liters, and \(Na_{in}\) is the sodium concentration in mmol/L. \(Na_{in}\) was not corrected for glucose concentration or for pH value.

Sodium removal corrected for ultrafiltration \((NaR/UF, \text{mmol/L})\) was calculated by the ratio of NaR and UF.

Statistical methods

The results are expressed as mean values ± SD for normally distributed variables and median values with interquartile ranges for asymmetrically distributed variables.

The effects of the glucose concentration and pH of the PD solutions on NaF\(_d\) and NaE\(_d\) and the difference between them were evaluated by means of linear regression analysis (in vitro study).

Repeated-measure analysis of variance was used to assess the evolution of D/PNaF and D/PNaE over time during PET (in vivo study). The paired t-test and Wilcoxon’s rank-sum test were used for the normal and asymmetrically distributed variables in order to compare the sodium removal estimated by F and E.

In vitro study

The linear regressions of the NaE\(_d\) and NaF\(_d\) values relating to the glucose concentration and pH of the PD solutions are shown in Figures 1 and 2, respectively.

At increasing glucose concentration values, the linear regression of Na\(_d\) to glucose concentration showed that NaE\(_d\) progressively increased, whereas NaF\(_d\) progressively decreased (Fig. 1). The linear regression of Na\(_d\) to pH showed that NaE\(_d\) progressively decreased at increasing pH values, whereas NaF\(_d\) did not change (Fig. 2).

In vivo study

The D/D1’ glucose ratio and the D/P creatinine and urea ratios (corrected for plasma water) at 240 minutes were 0.24 ± 0.07, 0.77 ± 0.10, and 0.90 ± 0.04, respectively.

The NaF and NaE dialysate and plasma glucose concentrations are shown in Table 2.
As in the in vitro study, the concentration of sodium in the two fresh PD solutions we used was significantly different when analyzed by F or by direct E. After 240 minutes of PET and in the overnight dialysate, the NaF\textsubscript{d} values were significantly higher than those of NaE\textsubscript{d}.

The initial pH in the fresh PD solutions was 5.745 ± 0.332, but it rapidly increased to 7.080 ± 0.189, 7.385 ± 0.068, 7.445 ± 0.048, and 7.518 ± 0.053 at Dt1\textsuperscript{9}, Dt60\textsuperscript{9}, Dt120\textsuperscript{9}, and Dt240\textsuperscript{9}, respectively.

The D/PNa ratio is shown in Figure 3. During the PETs, it was significantly lower when calculated as NaE (measured by direct E) than NaF (measured by F) at 1, 60, 120 and 240 minutes, but remained similar when calculated as NaE and NaF corrected for plasma water and a Donnan factor of 0.96.

As shown in Table 3, the NaF and NaE values of sodium removal during PET were significantly different, with the former being much higher than the latter.

The NaR/UF in the dialysate was hypotonic to the plasma water.

**DISCUSSION**

The relationship between plasma and dialysate sodium concentrations in hemodialysis has been clearly delineated elsewhere [3, 4].

The results of the present study show that the measurement of sodium concentrations and the relationship between NaF\textsubscript{d} and NaE\textsubscript{d} are more complex in peritoneal dialysis than in hemodialysis because of the higher and variable glucose concentration and the low pH of PD solutions.

As shown by our in vitro measurements in different PD solutions with variable glucose concentrations, the higher the glucose concentration, the higher the NaE\textsubscript{d} and the lower the NaF\textsubscript{d} value (Fig. 1). The NaF\textsubscript{d} value in fresh PD solutions does not depend on the pH value, whereas that of NaE\textsubscript{d} does (Fig. 2).

The flame photometer slightly underestimates actual sodium concentration in the presence of a high glucose concentration, and a low pH favors the dissociation of the ionized form of sodium measured by direct E; however, these factors are not sufficient to explain why the ionized sodium concentration in very acidic solutions measured by direct E is much higher than the total sodium measured by F. The real reason for this paradox is that the direct E used in our study is influenced by both the pH and glucose concentration values: in the presence of a high glucose concentration and a low pH, direct E overestimates sodium levels.

In conclusion, our in vitro study shows that a high glucose concentration only slightly affected the sodium measurements made using F and E, whereas a low pH has an important effect only on direct E sodium measurements, which in the case of very acidic solutions may be falsely high.

The initial pH of the acidic solutions, after the infusion in the peritoneal cavity, rapidly increased. This rapid neutralization led to a significant reduction in the NaE\textsubscript{d} value by eliminating the overestimate due to direct E and (partially) to the combination of sodium with lactate, bicarbonate, and other anions that occurs with increasing pH values.

The D/PNa ratio was statistically different when using F or direct E. The D/PNa was different because F measures the total plasma and dialysate sodium concentrations, whereas E measures the ionized (and not total) plasma water and dialysate sodium concentrations. The difference between the ionized (and not total) sodium concentrations in the plasma water and in the dialysate is the driving force for diffusion across membranes [7].

However, the difference in D/PNa ratio disappeared when the value of NaF\textsubscript{d} (measured by F) was corrected for plasma water and a Donnan factor of 0.96.

Sodium removal during PET was significantly lower when measured by direct E than when measured by F.

Real sodium removal is that measured by F because, despite the interference of high glucose concentrations, the overestimate is only about 4 mmol, whereas direct E considerably underestimates it because of the high glucose concentration and low pH of fresh PD solutions. If we had studied sodium removal using only direct E, we would have considerably underestimated the actual amount, but F measures actual sodium removal despite its slight underestimate of sodium concentration in fresh PD solutions.

The sodium removal measured by means of direct E was lower than that measured by means of F because direct E overestimates the sodium concentration in fresh PD solutions (Na\textsubscript{d}In) for the reasons mentioned pre-
Table 2. Plasma and dialysate glucose and sodium concentrations measured by means of a flame photometer (NaF) and a direct ion-selective electrode (NaE) in 66 PETs

<table>
<thead>
<tr>
<th></th>
<th>Glucose mg/dL</th>
<th>NaF mmol/L</th>
<th>NaE mmol/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma</td>
<td>88 (81–97)</td>
<td>139.2 (137.7–141.4)</td>
<td>141.8 (140.2–144.2)</td>
</tr>
<tr>
<td>Plasma water</td>
<td></td>
<td>148.8 (147.0–151.3)</td>
<td></td>
</tr>
<tr>
<td>Fresh dialysate</td>
<td>3675 (3585–3780)</td>
<td>132.1 (129.3–137.5)</td>
<td>138.0 (134.4–141.5)</td>
</tr>
<tr>
<td>Dialysate at 240 minutes</td>
<td>735 (573–910)</td>
<td>129.9 (126.3–136.4)</td>
<td>127.2 (123.8–132.6)</td>
</tr>
<tr>
<td>Overnight dialysate</td>
<td>227 (167–293)</td>
<td>139.2 (136.2–141.6)</td>
<td>135.3 (132.1–132.0)</td>
</tr>
</tbody>
</table>

Data are median values (interquartile ranges).

*P < 0.0001 vs. NaE

![Fig. 3. The dialysate and plasma sodium concentration ratio (D/PNa) during the peritoneal equilibration tests (PETs).](image)

**Fig. 3.** The dialysate and plasma sodium concentration ratio (D/PNa) during the peritoneal equilibration tests (PETs). *NaF vs. NaE: P < 0.0001; **NaE vs. NaFpwD: P < 0.3473. NaE is the D/P sodium ratio measured by means of a direct ion-selective electrode; NaF is the D/P sodium ratio measured by means of a flame photometer and corrected for pw and a Donnan factor of 0.96. Symbols are: (▲) NaF; (■) NaE; (●) NaFpwD.

Table 3. NaF and NaE sodium removal (NaR) at the end of 66 PETs

<table>
<thead>
<tr>
<th>NaRF</th>
<th>NaRE</th>
<th>NaRF/UF</th>
<th>NaRE/UF</th>
</tr>
</thead>
<tbody>
<tr>
<td>610 ± 32.2</td>
<td>43.9 ± 32.7</td>
<td>126.6 (102.7–138.5)</td>
<td>87.2 (68.3–110.3)</td>
</tr>
</tbody>
</table>

NaRF/UF and NaRE/UF represent Na removal per liter of ultrafiltrate. Data are mean ± SD or median (interquartile ranges).

*NaRF vs. NaRE, P < 0.0001

**REFERENCES**