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Appendix

Correction of sodium sieving for diffusion from the circulation

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Abstract
Transcellular water transport (TCWT) can be estimated by Na\(^+\) sieving. However, the assumption that the initial Na\(^+\) dialysate concentration (D0) is equal to the initial plasma concentration (P0) is not true for each patient. The difference leads to Na\(^+\) diffusion from the circulation to the dialysate, which diminishes the Na\(^+\) sieving.

A model was developed to distinguish transcellular water transport from Na\(^+\) diffusion. We previously found evidence that the mass transfer area coefficient of urate (MTAC\(_{\text{urate}}\)) was similar to the MTAC\(_{\text{Na}}\). The MTAC is the product of the elimination constant (k\(_e\)) and the volume of distribution (V\(_D\)), the mean intra peritoneal volume. Because V\(_D\) is known, the k\(_e\)Na\(^+\) in each patient can be equated with the k\(_e\)urate. The Na\(^+\) mass transfer from the circulation to the dialysate by diffusion can then be calculated for any time point during a dwell (D\(_t\)). D\(_t\) was subtracted from the measured Na\(^+\) dialysate concentration at 60 minutes. The corrected D/P Na\(^+\) then represents the actual Na\(^+\) sieving.

Using 3.86% glucose dialysate, this approach was investigated in 15 stable peritoneal dialysis (PD) patients (normUF) and 9 PD patients with low ultrafiltration (lowUF, <400 mL/4-hour). The MTAC\(_{\text{urate}}\) was calculated according to Waniweski (W) and according to the Garred model (G). Similar calculations were also performed for the MTAC for creatinine (MTACcreat). Initial D/P Na\(^+\) was not different between the groups. When no diffusion correction was made, D/P\(_{60}\) Na\(^+\) in the lowUF group (median 0.898, range 0.870-0.949) was significantly higher (p<0.025) than D/P\(_{60}\) Na\(^+\) in the normUF group (median 0.881, 0.816-0.899). The difference disappeared after diffusion correction regardless of the correction model applied. However, at 240 minutes, D/P Na\(^+\) in the normUF group was significantly lower than in the lowUF group (median 0.880, range 0.839-0.952 vs median 0.942, range 0.866-0.987; p<0.004). Even after correction, D/P Na\(^+\) in the normUF group was significantly lower: 0.847 normUF vs 0.893 lowUF (W\(_{\text{urate}}\), p<0.005); and 0.842 normUF vs 0.890 lowUF(G\(_{\text{creat}}\), p<0.003).

The correlation between the W\(_{\text{urate}}\) (the best theoretical diffusion correction) and G\(_{\text{creat}}\) (the least) was: y=0.99x+0.0037. Furthermore, Bland and Altman analyse of W\(_{\text{urate}}\) and G\(_{\text{creat}}\) at both 60 and 240 minutes resulted in random distribution around the means, with a slight overestimation in relation to the magnitude of G\(_{\text{creat}}\), as was expected. G\(_{\text{creat}}\) can be used to make an accurate estimation of the contribution of Na\(^+\) diffusion in the time course of D/P Na\(^+\). It provides a simple way to more precisely determination of Na\(^+\) sieving, and therefore of TCWT.

In conclusion, to avoid overestimation of impaired channel-mediated water transport, a Na\(^+\) diffusion correction should be made when D\(_0\) is not equal to P\(_e\) or in the case of a large vascular surface area.

Introduction
Low ultrafiltration is a major reason for therapy drop-out from peritoneal dialysis therapy, especially in long-term peritoneal dialysis [1-4]. Impaired ultrafiltration-defined as net ultrafiltration <400 mL/4-hour with a 3.86% glucose dialysis
solution is regarded as clinically important ultrafiltration failure [3]. The causes can be either mechanical— for example, subcutaneous leaks or a large residual volume— or related to the peritoneal membrane itself. The latter group includes the presence of a large peritoneal vascular surface area, a high effective lymphatic absorption rate, impaired transcellular (aquaporin-mediated) water transport (TCWT), or combinations of these.

TCWT can be estimated by the sieving of sodium. Sieving of sodium is defined as the dip in the dialysate-over-plasma ratio (D/P) of sodium that occurs during a dialysis exchange with a 3.86% glucose solution [2,3,5,6]. Sodium sieving is especially pronounced during the initial phase of the dwell, when water transport has its maximum value [7]. The magnitude of this dissociation of Na' and water transport provides information on aquaporin-mediated water transport, for it is likely that the decrease in the dialysate concentration of Na' in first 60 minutes is caused by channel-mediated water transport, which is provoked by a large osmotic gradient. However, this dip in D/P Na' can be influenced by diffusion of sodium from the circulation to the dialysate. Correction for this diffusion should be considered in case of a large vascular peritoneal surface area, especially in the situation where the plasma Na' concentration is substantially higher than the dialysate concentration. In the presence of a large vascular surface area, diffusion of Na' from the circulation to the dialysate will increase, thereby blunting the D/P Na' dip and overestimating the impairment of TCWT.

The actual contribution of TCWT can be calculated by subtracting the peritoneal sodium gradient obtained with 1.36% glucose from the peritoneal sodium gradient obtained with 3.86% glucose [8]. This correction is based on the assumption that convective transport of Na' during a 1.36% dwell is approximately similar [7] to the fluid-accompanied sodium absorption from the peritoneal cavity to the interstitium and the circulation, neutralizing the convective transport of Na'. The simplicity of this method is countered by the fact that two tests have to be performed in each patient. The aim of the present study was, therefore, to develop a simple model to correct the TCWT-induced dip in the dialysate sodium concentrations from sodium diffusion, using only one 3.86% glucose exchange.

**Methods**

**Rationale**

The mass transport of solutes across the peritoneal membrane is a combination of convection and diffusion. Diffusional transport is determined by the product of the mass transfer area coefficient (MTAC) and the concentration gradient of the solute between plasma and dialysate. The MTAC is the maximal theoretical clearance by diffusion at time 0, before diffusion has actually started.

We previously found that the average MTAC\(_{\text{Na}^+}\) was similar to the MTAC\(_{\text{urate}}\), namely 8.3 mL/min [9]. Also, a good correlation was present between the MTAC\(_{\text{urate}}\) and the MTAC\(_{\text{Na}^+}\) (n=10, r=0.84, p<0.0026). Consequently, the MTAC\(_{\text{urate}}\) can be used to predict the concentration gradient of Na' by diffusion, because the initial concentration gradient of sodium is known. However, urate is not typically measured on a routine basis, as creatinine is.
The correlation between MTAC\textsubscript{creat} and MTAC\textsubscript{Na}, was also strong in the study of Imholz et al. \((n = 10, r = 0.91, p < 0.00028)\). The mean MTAC\textsubscript{creat} is 11 mL/min [9,10]. Some overestimation of diffusive sodium transport can therefore be expected when the MTAC\textsubscript{creat} is used instead of MTAC\textsubscript{urea}. The dialysate Na\textsuperscript{+} concentration can be calculated at any time point during the dwell by subtracting, from the measured gradient, the estimated concentration gradient of Na\textsuperscript{+} by diffusion. The sieving of Na\textsuperscript{+} is then obtained by converting the corrected Na\textsuperscript{+} gradient into a D/P ratio.

\textit{Description of the model}

The MTAC can be determined by complicated numerical models and by more simple analytical models [11]. Most of the analytical models use integrative procedures for solving the differential equations. One of these is the Garred model [12]. However, the same equation as derived by Garred et al. was obtained using the pharmacokinetic principle of first-order kinetics [13]. In this approach, the MTAC is defined as the product of the elimination constant \(k_e\) and the volume of distribution \(V_D\):

\[
\text{MTAC} = k_e V_D
\]  

\(k_e\) is the elimination constant of the product of the concentration gradient and the intraperitoneal volume. The mean intraperitoneal volume during the dwell is used for \(V_D\), which is determined by the area under the intraperitoneal volume-versus-time curve divided by the dwell time [14]. The basis equation of first-order kinetics from which \(k_e\) can be calculated is:

\[
\ln V_i(P_m - D_i) - k_e t \cdot \ln V_i(P_m - D_i) = k_e V_D
\]

in which \(P_m\) is the mean plasma concentration, \(P_m - D_i\) is the concentration gradient at time 0, \(P_m - D_i\) is the concentration gradient at time \(t\), \(V_0\) is the intraperitoneal volume at time 0, and \(V_i\) is the intraperitoneal volume at time \(t\). Equation (ii) can be rearranged to:

\[
-k_e t \cdot \ln V_i(P_m - D_i) = \ln V_i(P_m - D_i)
\]

Multiplication of both terms in (iii) with \(V_i/t\) yields:

\[
-k_e V_D \ln V_i(P_m - D_i) = \frac{\ln V_i(P_m - D_i)}{V_i}
\]

The left term in equation (iv) represents the MTAC according to the principle given in equation (i). This left term of equation (iv) can now be replaced by the MTAC\textsubscript{creat}, which could have been obtained by various methods (see below), and is assumed to be equal to the MTAC\textsubscript{Na}.
This substitution is summarized in the equation:

\[
MTAC_{urate} = MTAC_{na} = V \int_0^t \left[ lnV_0(P_{Na^+0} - D_{Na^+0}) - lnV_t(P_{Na^+m} - D_{Na^+0}) \right]
\]  

in which \( P_{Na^+0} \) and \( D_{Na^+0} \) represent the plasma and dialysate concentrations of sodium at time 0; \( D_{Na^+t} \) the \( Na^+ \) dialysate concentration at time \( t \); and \( P_{Na^+m} \), the mean plasma concentration of sodium. Because \( V_0, V_1 \), and \( V_0 \) are not different for urate and \( Na^+ \), and because \( P_m \) and \( D_0 \) are known for \( Na^+ \), \( D_t \) of \( Na^+ \) caused by diffusion can be calculated at any time point during the dwell. Subtracting the measured \( D_0 \) from the calculated \( D_t \) results in the estimated increase by diffusion. This value is subtracted from the measured \( Na^+ \) dialysate concentration, yielding the \( Na^+ \) dialysate concentration at time \( t \) when no diffusional transport would have occurred. The corrected \( D/P \) \( Na^+ \) then represents the actual sieving of sodium at time \( t \). This approach was also investigated by applying the MTAC according to Waniewski (see appendix of this chapter) [15-17].

Table 1. Peritoneal solute and fluid kinetics in the two patient groups (median and ranges).

<table>
<thead>
<tr>
<th></th>
<th>normal ultrafiltration</th>
<th>low ultrafiltration</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=15</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MTAC_{urate (mL/min)}</td>
<td>6.67 (4.12-10.01)</td>
<td>8.99 (5.84-16.18)</td>
<td>p&lt;0.0035</td>
</tr>
<tr>
<td>MTAC_{rest (mL/min)}</td>
<td>8.50 (5.95-11.55)</td>
<td>12.07 (7.19-19.06)</td>
<td>p&lt;0.0035</td>
</tr>
<tr>
<td>DP_0-D_0 (mmol)</td>
<td>8 (4.13)</td>
<td>8 (6.14)</td>
<td>ns</td>
</tr>
<tr>
<td>ELAR (mL/min)</td>
<td>1.14 (-0.31-2.03)</td>
<td>1.57 (-0.28-5.21)</td>
<td>ns</td>
</tr>
<tr>
<td>TCUFR (mL/min)</td>
<td>4.08 (2.18-6.37)</td>
<td>2.95 (0.09-3.98)</td>
<td>p&lt;0.02</td>
</tr>
<tr>
<td>NUF (mL/4 hour)</td>
<td>553 (435-1199)</td>
<td>46 (-290-389)</td>
<td>p&lt;0.0007</td>
</tr>
<tr>
<td>RV (mL)</td>
<td>253 (111-604)</td>
<td>215 (28-392)</td>
<td>ns</td>
</tr>
</tbody>
</table>

ELAR = effective lymphatic absorption rate, TCUFR = transcapillary ultrafiltration rate, NUF = net ultrafiltration, RV = residual volume. MTACs were calculated according to Waniewski. \( DP_0-D_0 \) is the difference between the initial \( Na^+ \) concentration in plasma \( (P_0) \) and dialysate \( (D_0) \).

Figure 1. Median values of the measured \( D/P \) \( Na^+ \) (solid line), the measured \( D/P \) \( Na^+ \) corrected with the Waniewski urate model (dashed line), and the measured \( D/P \) \( Na^+ \) corrected with the simplified Garred creatinine model (dotted line) are plotted against the dwell time. The left panel shows normUF patients, and the right panel, lowUF patients.
Correction of Na\(^+\) sieving for diffusion

Application of the model
The above approach was investigated in 15 stable PD patients with normal ultrafiltration and in 9 patients with low ultrafiltration. Low ultrafiltration was defined as net ultrafiltration <400 mL/4-hour after a hypertonic exchange using 3.86% glucose dialysis solution [3]. Peritoneal permeability characteristics were studied with a standard peritoneal permeability analysis using 3.86% glucose-containing dialysis solution during a 4-hour dwell. The procedure and the calculations of fluid and solute transport have been described previously [10,18]. The MTACs of urate and creatinine were both investigated. These MTACs were calculated according to both the simplified Garred model [13] and the more precise Waniek model [15,16]. In the latter model, solute concentrations in plasma are expressed per volume of plasma water using the total protein concentration in plasma, and a correction factor for convection is also applied [16]. The assumption was made that the elimination constants and the MTACs would not change throughout the dwell.

Mann-Whitney tests and Spearman rank correlation tests were used for distribution free testing. The four different correction models were compared using a Bland and Altman analysis [14] to investigate possible systematic errors.

Results
The characteristics of peritoneal solute and fluid kinetics obtained in the normal ultrafiltration patients (normUF) and the low ultrafiltration patients (lowUF) are summarized in Table 1. The possible reasons for the low ultrafiltration in the latter group were: a high effective lymphatic absorption, defined as >2 mL/min (n=3); a large vascular peritoneal surface area, defined as MTAC\(_{\text{urea}}\) > 13.0 mL/min (n=4); a large residual volume, defined as >350 mL (n=2); or no reason was found (n=2). Combinations of two possible causes were found in 2 patients. The definitions for abnormal effective lymphatic absorption rates, large vascular peritoneal surface area, and large residual volume are derived from Pannekeet et al. [3,10].

The initial D/P Na\(^+\),0 was not different between the groups: normUF median 0.936 (range: 0.908-0.966), and lowUF median 0.945 (range: 0.897-0.956). Also, the plasma and dialysate concentrations at time 0 were not significantly different between the groups (Table 1). The lowUF patients had lower uncorrected D/P Na\(^+\) than the normUF patients, at both 60 minutes (p<0.025) and 240 minutes (p<0.004).

The effect of correcting the sieving of sodium with each of the four models is presented in Table 2. No significant differences were present between the corrected D/P Na\(^+\) values obtained with any of the models within either ultrafiltration group at both 60 and 240 minutes. After correction with all four models, the D/P Na\(^+\) values in the normUF group were significantly lower than those in the lowUF group at 240 minutes. However, after correction, the D/P Na\(^+\) values at 60 minutes were similar for each of the four models in both the normUF and the lowUF group. Figure 1 shows the effects of correcting D/P Na\(^+\) for diffusion during the 4-hour dwell period using the MTAC\(_{\text{urate}}\) Waniek model (theoretically the best model)

\[\text{D/P Na}^+ \]
The differences among the four models within the normal and low utilization groups were not significant at either 60 or 240 minutes. The Wainewright model, however, was significantly different from the other models at both time points. The Wainewright model was consistent with the results from the MAC aid model, which suggests that the Wainewright model may be a good approximation of the MAC aid model.

<table>
<thead>
<tr>
<th>Model</th>
<th>60 Minutes</th>
<th>240 Minutes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>0.825</td>
<td>0.995</td>
</tr>
<tr>
<td>Low</td>
<td>0.855</td>
<td>0.989</td>
</tr>
</tbody>
</table>

Table 2: Estimation of sodium steve with Na diffusion correction
and using the MTAC\text{creat} simplified Garred model (the least accurate, but more easily applicable model) applied over both ultrafiltration groups. The relationships and analyses of agreement between the four correction models were investigated at time 60 and 240 minutes. The relationships between the best and the least model at these timepoints are shown in Figure 2. The correlations were excellent at both time points ($r_{60} = 0.999$, $p_{60} < 1.99 \cdot 10^{-30}$, $r_{240} = 0.996$, $p < 1.99 \cdot 10^{-24}$). This result suggests that the correction model using Waniewski MTAC\text{ur} may be substituted by the model using the Garred MTATC\text{creat}.

Bland and Altman analyses of these two models at both time points are presented in Figure 3. The corrected D/P Na$^+$,60' ratios of both ultrafiltration groups together show a random distribution between the mean and differences of D/P Na$^+$,60' according to the Waniewski MTAC\text{ur} model and the model calculated according to simplified Garred MTAC\text{creat}. The overestimation of Na$^+$ diffusion from the circulation when the simplified Garred MTAC\text{creat} is applied is reflected in the shift of the difference between the means of the two methods of correction to 0.0017 for D/P Na$^+$,60' and 0.0019 for D/P Na$^+$,240'. These shifts are marginal, which implies that negligible systematic errors are present relative to the magnitude of the parameters. The 95% confidence interval was wider at time 240 minutes. These results imply a close agreement between both extremes of the correction methods.

Discussion

The decrease in dialysate sodium concentration owing to the substantial sieving of sodium during the initial phase of a hypertonic dwell with 3.86% glucose dialysis solution has been suggested as an estimation of transcellular water transport [3,5]. Impairment of this aquaporin-mediated water transport can be a possible cause of low peritoneal ultrafiltration. Therefore, accurate estimation of sodium sieving is valuable for the analysis of loss of peritoneal ultrafiltration capacity. The sodium balance during peritoneal dialysis depends on diffusive transport, convection across the peritoneal membrane, and fluid absorption from the peritoneal cavity to the interstitium and the circulation. Diffusional transport is determined by the product of the MTAC and the concentration gradient of the solute between plasma and dialysate. Because the concentration gradient in individuals can range between 0 mmol/L and 15 mmol/L, the contribution of diffusion can have a considerable variability. In situations with relatively high diffusion rates, the sieving of sodium will be blunted.

In this study, the assumption was made that the average MTAC$_{\text{Na+}}$ was in the same order of magnitude as the MTAC$_{\text{ur}}$ and MTAC$_{\text{creat}}$[7,9,19,20]. Creatinine is typically measured on a routine basis, but urate is not. However, because the MTAC$_{\text{creat}}$ is higher than that of sodium, an overcorrection of the sodium diffusion from the circulation could be expected, leading to an overestimation of the sieving of sodium. Investigating this with a Bland and Altman analysis, the difference between means of D/P Na$^+$ corrected with the Waniewski urate model or with the simplified Garred creatinine model appeared negligible. Furthermore, the data were randomly distributed around the mean, suggesting that no systematic errors were
Figure 2. The relationship between the best model (Wernerswold model) and the least (simplified cardiac ejection model)

\[ \text{MTAC}_{\text{corrected}} = \text{MTAC}_{\text{measured}} \]

Triangles represent the normal group, and closed circles represent the normal group, and closed circles represent the abnormal group.
Figure 3: Bland and Altman analyses of the best correction model and the least at 60 minutes (left panel) and 240 minutes (right panel). Relative to the magnitude of the parameters, no systematic errors are present. The data are randomly distributed around the mean. Closed circles represent the normal UP group, and closed triangles, the low UP group.
present between the two models. However, others stated that the mass transfer of sodium does not occur in a manner similar to that of urate and creatinine [7,17,19,20]. These authors found that the diffusion of sodium was considerably slower than that of urea, creatinine, and glucose, taking molecular weight into account. The underlying mechanism was not explained.

The four different models investigated in this study are based on two calculation methods for mass transfer area coefficients for both urate and creatinine. The Waniewski model corrects the plasma concentration to aqueous plasma concentration, taking the presence of lipids and proteins in plasma into account, and corrects for Donnan equilibrium of small cations between dialysate and plasma (see appendix of this chapter) [16]. The simplified Garred model assumes that the interdependence between convective and diffusive transport of a solute, represented by $F$, is zero [12], while the Waniewski model corrects for convection by applying an $F$ of 0.5 (see appendix of this chapter). Another important difference between the models is that the Garred model assumes the sieving coefficient to be 1, while Wang et al. [7] calculated a sieving coefficient for sodium of 0.61 [17]. Although the simplified Garred model may be less correct than the Waniewski model, it is more easily applicable. Values obtained with a standard peritoneal equilibration test are sufficient to calculate the MTAC$_{\text{crea}}$ using the simplified Garred model [13]. Furthermore, the error associated with the assumptions made in the Garred model approaches zero for small solutes [12]. Even if principle differences exists between the two correction methods, the differences appear negligible, as the data were randomly distributed around the mean.

We compared the 95% confidence intervals at 60 and 240 minutes. The interval at 240 minutes was wider than that at 60 minutes. A possible explanation is that the ultrafiltration rate levels off during the last phase of the dwell when osmotic gradient has decreased. This possibility is not taken into account in any of the models, because the MTACs and the $k_c$ were assumed to stay identical throughout the dwell. This is of interest especially in patients with a large peritoneal vascular surface area, because, in their case, overestimation of the correction would be more pronounced at the end of the dwell, eventually leading to a wider scatter of the differences between the means of the MTAC$_{\text{ur}}$ ($W$) and the MTAC$_{\text{crea}}$ ($G$). This is not the case at 60 minutes, as ultrafiltration is still increasing at that time point. Furthermore, the minimum value of the D/P Na$^+$ is often reached after approximately 60 minutes, suggesting that the corrected D/P Na$^+$ at 60 minutes might be the preferable one to use in estimating transcellular water transport.

Wang et al. [7] suggested determining D/P Na$^+$ at the end of the dwell. At this time point, a distinction could be made between the various transport groups (low, low average, high average, high), which was not possible at 60 minutes when the D/P Na$^+$ was used. However, the objective of that study was to classify patients into transport categories, while the aim of the present study was to improve the accuracy of sodium sieving as a measurement of channel-mediated water transport.

The present study describes a simple and a more sophisticated model to distinguish the transcellular water transport-induced decrease in the dialysate
sodium concentration from sodium diffusion during the initial phase of a hypertonic dwell. No essential differences were found between the correction methods, although they were derived differently and used either urate or creatinine as reference solutes. Further studies comparing these models with other correction methods are necessary to establish their place in the assessment of aquaporin-mediated water transport.

Appendix
The following equations are applied for calculating the MTACurate and MTACcreatinine according to Wanieński et al. [15-17] to determine $k_u$ urate and $k_c$ creatinine:

$$ MTAC_{uran} = \frac{V}{t} \cdot \ln \left( \frac{T_{10}}{V_m} \cdot \frac{(P_o \cdot x_o - P_r \cdot x_f)}{2} \cdot D \right) $$

in which a correction factor for convective transport ($F$) of 0.5 is applied. Furthermore, the concentration of a solute per plasma water is related to its concentration per whole plasma ($x_o$ and $x_f$).

The factional volume of plasma lipids ($1-0.016=0.984$) and the plasma concentration of total protein ($TP$) are taken into account.

$$ x_o^o = \frac{1}{(0.984-0.000718 \cdot TP_0)} $$

$$ x_f^o = \frac{1}{(0.984-0.000718 \cdot TP)} $$

$TP_0$ is the plasma concentration of total protein at time 0, and $TP$, is the plasma concentration of total protein at time t.

References
Appendix
