ASN DIALYSIS ADVISORY GROUP

ASN DIALYSIS CURRICULUM
AN UPDATE ON UREMIC TOXICITY:
Part 1

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Disclosures

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BASIC PRINCIPLES OF HEMODIALYSIS AND ITS IMPACT ON SOLUTE REMOVAL
DIFFUSION VS. CONVECTION

DIFFUSION

CONVECTION
IMPACT OF LOW-FLUX DIALYSIS ON DIFFERENT TYPES OF UREMIC TOXINS

- Small water soluble compound
- Middle molecule
- Protein bound compound
- Free protein bound compound
IMPACT OF HIGH-FLUX DIALYSIS ON DIFFERENT TYPES OF UREMIC TOXINS

- small water soluble compound
- middle molecule
- protein bound compound
- free protein bound compound
IMPACT OF HEMODIAFILTRATION ON DIFFERENT TYPES OF UREMIC TOXINS

- small water soluble compound
- middle molecule
- protein bound compound
- free protein bound compound
UREMIC SOLUTE KINETICS HAS A MAJOR IMPACT ON THEIR REMOVAL

**FIGURE:** Two-compartment kinetic model. $V_1$: plasmatic volume, $V_2$: extraplasmatic volume, $C_1$: plasmatic concentration, $C_2$: extraplasmatic concentration, $MT_{dialyser}$: mass transfer in the dialyser, $K_{21}$: intercompartment clearance, $G$: solute generation.

Eloot et al, NDT, 27:4021-4029; 2012
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Eloot et al, NDT, 27:4021-4029; 2012
3x4h \( Q_B \ 300 \)  \hspace{1cm} 6x2h \( Q_B \ 300 \)  \hspace{1cm} 3x8h \( Q_B \ 200 \)

**STEEP INITIAL DECLINE**

**C_1** \hspace{1cm} **C_2**

**SLOWER SUBSEQUENT DECLINE**

**REBOUND**

**B2M concentration (mg/L)**

**time (min)**
Summary

• **In vitro effect**

• **In vivo effect**

• **Removal of small molecules**
  • Analytical data on adequacy
  • Clinical outcomes

• **[Removal of protein-bound and middle molecules covered in Uremic Toxins: part 2]**


Urea
Effect of increasing dialysate urea

This figure was published in Mayo Clin Proc, 47, Johnson et al., Effects of urea loading in patients with far-advanced renal failure, 21-29. Copyright Elsevier (1972).
UREA DISRUPTS INTESTINAL WALL PROTECTIVE BARRIER

Figure 1
Bar graphs depicting the TER (transepithelial electrical resistance) in intestinal epithelial T84 cell monolayers incubated for 24 h in regular media and those incubated in media containing 42 or 72 mg/dl urea. *** p < 0.001.

UREA INDUCES INSULIN RESISTANCE

Urea causes decreased insulin sensitivity in differentiated 3T3L1 adipocytes. (A) Effect of urea on insulin-stimulated glucose uptake in differentiated 3T3L1 cells.

D’Apolito et al, J Clin Invest, 120: 203-213; 2010

Will need to remove or alter as re-use fee is $41
TRANSPORT OF UREA AND ANALOGUES VIA ERYTHROCYTE CELL WALL

Erythrocyte solute permeability measured by stopped-flow light scattering. (A) Representative curves for the time course of scattered light intensity at 10 °C in response to a 250mM inwardly directed gradient of urea analogues. (B) Averaged solute permeability coefficients (Ps) for experiments done as in panel A (mean ± S.E., n=3).

This figure was published in Biochim Biophys Acta, 1768, Zhao et al., Comparative transport efficiencies of urea analogues through urea transporter UT-B, 1815-1821. Copyright Elsevier (2007).
## Solute Concentration Correlates with Renal Function and Protein Intake (Not Kt/V)

<table>
<thead>
<tr>
<th>Solute</th>
<th>Covariates / R² full model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urea</td>
<td>nPCR / 0.850</td>
</tr>
<tr>
<td>Crea</td>
<td>nPCR / 0.150</td>
</tr>
<tr>
<td>Uric acid</td>
<td>nPCR / 0.195</td>
</tr>
<tr>
<td>beta-2-microglobulin</td>
<td>nPCR / 0.172</td>
</tr>
<tr>
<td>Hippuric acid</td>
<td>nPCR / 0.187</td>
</tr>
<tr>
<td>Indoxyl sulfate</td>
<td>nPCR / 0.059</td>
</tr>
<tr>
<td>p-cresylsulfate</td>
<td>nPCR / 0.268</td>
</tr>
<tr>
<td>p-cresylglucuronide</td>
<td>RRF / 0.134</td>
</tr>
<tr>
<td>Free hippuric acid</td>
<td>RRF / 0.206</td>
</tr>
<tr>
<td>Free indoxyl sulfate</td>
<td>RRF / 0.144</td>
</tr>
<tr>
<td>Free indole acetic acid</td>
<td>RRF / 0.166</td>
</tr>
<tr>
<td>Free p-cresylsulfate</td>
<td>nPCR / 0.189</td>
</tr>
<tr>
<td>Free p-cresylglucuronide</td>
<td>RRF / 0.135</td>
</tr>
</tbody>
</table>

Model: age, gender, nPCR, Kt/V, RRF, diabetes, body weight, vintage

Eloot et al, Plos One, 8:e76838; 2013
ADMA + SDMA
GUANIDINO COMPOUNDS
### ADMA CONCENTRATION IS LINKED TO MORTALITY

<table>
<thead>
<tr>
<th>Concentration of ADMA (percentile)</th>
<th>Number of patients *</th>
<th>Hazard ratio ** (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 50 th</td>
<td>33/113 (29%)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>50-75 th</td>
<td>22/56 (39%)</td>
<td>1.72 (1.00-2.97)</td>
<td>0.05</td>
</tr>
<tr>
<td>&gt; 75 th</td>
<td>28/56 (50%)</td>
<td>3.11 (1.83-5.27)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Fatal and non-fatal cardiovascular events</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 50 th</td>
<td>29/113 (26%)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>50-75 th</td>
<td>25/56 (45%)</td>
<td>2.13 (1.24-3.65)</td>
<td>0.006</td>
</tr>
<tr>
<td>&gt; 75 th</td>
<td>27/56 (48%)</td>
<td>2.80 (1.63-4.81)</td>
<td>0.0002</td>
</tr>
</tbody>
</table>

ADMA = asymmetric dimethylarginine  
* Denominator represents number of patients at risk  
** Adjusted for age and sex

Zoccali et al., Lancet, 358: 2113-2115; 2001
ADMA HAS IN VOLUNTEERS A MARKED HEMODYNAMIC EFFECT

Effect of 0.10 mg ADMA \(\text{dot} \text{kg-1 \text{dot} \text{min-1}}\) on cardiac output (A) and systemic vascular resistance (SVR) (B) in 7 healthy volunteers.

Kielstein et al., Circulation, 109: 172-177; 2004
SDMA INDUCES IN VITRO CYTOKINE GENERATION

Schepers et al, CJ ASN, 6: 2374-2383; 2011
Variables associated with the serum levels of SDMA and ADMA by linear regression

Schepers et al, CJ ASN, 6: 2374-2383; 2011
MOST GUANIDINES ARE DISTRIBUTED OVER A LARGER COMPARTMENT THAN UREA

<table>
<thead>
<tr>
<th>Compound</th>
<th>V</th>
<th>Eff Rem</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urea</td>
<td>42.7±6.0</td>
<td>67±4</td>
</tr>
<tr>
<td>Creatine</td>
<td>98.0±52.3*</td>
<td>42±16*</td>
</tr>
<tr>
<td>Creatinine</td>
<td>54.0±5.9*</td>
<td>58±6*</td>
</tr>
<tr>
<td>Guanidino acetic acid</td>
<td>123.8±66.9*</td>
<td>37±14*</td>
</tr>
<tr>
<td>Guanidine</td>
<td>89.7±21.4*</td>
<td>43±7*</td>
</tr>
<tr>
<td>Methylguanidine</td>
<td>102.6±33.9*</td>
<td>42±12*</td>
</tr>
</tbody>
</table>

*: p<0.05; V: distribution volume (L); Eff Rem: effective removal (%);

Eloot et al., KI, 67: 1566-1575; 2005
A SOLUTION TO THIS PROBLEM IS MODIFYING THE TIMEFRAME OF DIALYSIS

<table>
<thead>
<tr>
<th></th>
<th>Reference</th>
<th>3x8_150</th>
<th>3x8_200</th>
<th>6x2_300</th>
<th>6x8_200</th>
<th>3x4_350</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Urea</strong></td>
<td>645 ± 180</td>
<td>682 ± 172</td>
<td>760 ± 200</td>
<td>733 ± 175*</td>
<td>1137 ± 307*</td>
<td>668 ± 173</td>
</tr>
<tr>
<td><strong>GSA</strong></td>
<td>0.175 ± 0.071</td>
<td>0.186 ± 0.065</td>
<td>0.206 ± 0.072*</td>
<td>0.202 ± 0.072*</td>
<td>0.298 ± 0.104*</td>
<td>0.176 ± 0.063</td>
</tr>
<tr>
<td><strong>CREA</strong></td>
<td>18 ± 5</td>
<td>21 ± 6*</td>
<td>24 ± 7*</td>
<td>21 ± 6*</td>
<td>36 ± 10*</td>
<td>20 ± 6*</td>
</tr>
<tr>
<td><strong>MG</strong></td>
<td>0.079 ± 0.042</td>
<td>0.091 ± 0.049*</td>
<td>0.111 ± 0.061*</td>
<td>0.089 ± 0.049*</td>
<td>0.179 ± 0.097*</td>
<td>0.093 ± 0.049*</td>
</tr>
</tbody>
</table>

* P <0.05, compared to reference dialysis

Eloot et al., NDT, 24: 2225-2232; 2009
See Uremic Toxins: part 2 for discussion of protein-bound and middle molecules
Conclusions

• Adequacy of removal of uremic solutes is hampered by characteristics of dialyzers and dialysis and by the multicompartmental distribution of most uremic toxins

• Removal can be enhanced by opening pore size and adding convection, but also by applying extended or frequent dialysis

• Urea, our current marker, of dialysis adequacy has long been considered to be inert but recent data may suggest a biological (toxic) effect

• ADMA and SDMA are guanidines with proven toxic effects

• Kinetics of urea are not representative for that of other water soluble compounds, like the guanidines