Sorbents for Uremic Toxins: Construction Delays in Our Roadmap

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Stephen R. Ash, MD, FACP
HemoCleanse Technologies LLC
Lafayette, Indiana
For Dialysis Devices to Be Implantable, Portable or Easily Transportable, We Must Remove Uremic Toxins from Dialysate

- Usual approach of “single pass” high-flow dialysate “washes” away uremic toxins from the membranes, but is impractical
- Regeneration of dialysate is preferred
  - Even if we could totally recover water from dialysate we would need large volumes of concentrate to make fresh dialysate
  - Sorbents are needed with specific binding for uremic toxins while avoiding excessive removal of vital salts and chemicals...
Our Roadmap Shows We May Have a Little Delay in Our Trip...
On Closer Inspection..
Maybe an Unexpected Big Delay
Today’s Talk

• Dialyate Sorbent Systems That Have Worked
  – Redy® (Sorb® ) Columns
• Potential Sorbent Systems for Urea/Ammonium
  – Zirconium Cyclo-Silicate
  – Liquid Membrane Capsules
  – Synthetic Zeolites (calcium loaded)
  – Electro-oxidation
• Role of Carbon in Removing Organic Uremic Toxins
• Removal of Small or Charged Uremic Toxins Within the Gut
  – Cation/Anion Exchangers for Removal of Small But Important Toxins (urea, potassium, hydrogen, sodium, phosphate)
What are Sorbents?

• Sorbents are chemicals or solids that bind other chemicals
• Includes “adsorbents” and “absorbents”
There are Four Classes of Sorbents:

- **Direct Sorption** (Van der Waals or Electrostatic)
- **Cation Exchange**
  - Cations *(Divalent preferred)*
- **Anion Exchange**
- **Antibody/Antigen**

![Diagram](image-url)
The Redy 2000 Dialysis Machine and Sorb Column
The “Sorbsystem” and “Redy 2000” Machines for use with the Redy (Sorb) column

- Was portable and usable in many environments
- Dual needle
- No ultrafiltration control
- Reinfusion of calcium/magnesium acetate to dialysate
- User creation of dialysate required at each treatment
- Machine production ended in 1994
- Over 2,000,000 safe patient treatments
- Some home dialysis patients were on treatment up to 2 years.
Sorbent-Based Hemodialysis Systems

After the Redy HemoCleanse and Renal Solutions (a Spin-Off)


Single or dual access, pressure actuated blood pumping, controlled filtration, automatic priming and rinse-back, automated ammonium monitor and everything else we could think of...
The Sorbent Cartridge

Cartridge Effluent

- Zirconium Oxide & Zirconium Carbonate Layer
  - Binds: Phosphate, Fluoride, Heavy Metals
  - Releases: Acetate, Bicarbonate (more), Sodium

- Zirconium Phosphate Layer
  - Binds: Ammonium, Calcium, Magnesium, Potassium, Metals, Other Cations
  - Releases: Sodium (less), Hydrogen, Ammonium Carbonate

- Urease Layer
  - Binds: Nothing (Converts Urea)
  - Releases: Nothing

- Activated Carbon & Purification Layer
  - Binds: Heavy Metals, Oxidants, Chloramine, Creatinine, Uric Acid, Other Organics, Middle Molecules
  - Releases: Nothing

Used Dialysate
Column Saturation with Ammonium Even Flow Results in Complete Usage of ZP Layer
Dialysate Preparation for the Redy 2000 Machine:
Culinary Medicine

**BICARBONATE DIALYSIS KITS**
The following BICARB KITS (Dialysates #1 and 2) offer instant bicarbonate dialysis. Fifteen minute recirculation through the cartridge is not necessary with dialysates made from BICARB KITS.

Each BICARBKIT Contains: Hydrochloric acid (1N), one pair Disposable Gloves (not to be used for infectious or disease control), one 12 ml disposable syringe, 48 g Dextrose, and one of the two following combinations of dry Dialysates.

<table>
<thead>
<tr>
<th>Dialysate</th>
<th>Description</th>
<th>Sodium Bicarbonate</th>
<th>Sodium Chloride</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NaHCO₃ DIALYSATE 1</strong></td>
<td>Provides 20 mEq/L sodium bicarbonate when added to 6 L water.</td>
<td>10 g</td>
<td>42 g</td>
</tr>
<tr>
<td><strong>NaCl DIALYSATE 1</strong></td>
<td>Provides 120 mEq/L sodium chloride when added to 6 L water.</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>NaHCO₃ DIALYSATE 2</strong></td>
<td>Provides 60 mEq/L sodium bicarbonate when added to 6 L water.</td>
<td>30 g</td>
<td>21 g</td>
</tr>
<tr>
<td><strong>NaCl DIALYSATE 2</strong></td>
<td>Provides 80 mEq/L sodium chloride when added to 6 L water.</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>NaCl DIALYSATE ADDITIVE</strong></td>
<td>Provides 20 mEq/L sodium chloride when added to 6 L water.</td>
<td>7 g</td>
<td></td>
</tr>
</tbody>
</table>

**DIALYSATE ADDITIVES**

**Dextrose**
Provides 4 g/L dextrose when added to 6 L dialysate. One or more packets should be added to any dialysate mixture. See Guide to Custom Dialysis* for additional information.

**NaHCO₃ ADDITIVE**
Provides an additional 10 mEq/L sodium bicarbonate when added to any of the NaHCO₃ dialysates (1 or 2).

**NaCl DIALYSATE ADDITIVE**
Provides 20 mEq/L sodium chloride when added to 6 L water.

**ASCORBIC ACID**
Sodium Chloride: 7 g

**INFUSATES**

**SORB™ 10 INFUSATE**
Provides 3.0 mEq/L calcium acetate and 1.0 mEq/L magnesium acetate when added to the Infusate Jar and delivered to the dialysate as specified above.

- Calcium Acetate: 32 g
- Magnesium Acetate: 13 g

**INFUSATE ADDITIVES**

**Ca-1/2**
Provides 0.5 mEq/L calcium acetate when added to infusate.

- Calcium Acetate: 5 g

**K-1**
Provides 1.0 mEq/L potassium acetate when added to infusate.

- Potassium Acetate: 12 g

**Mg Acetate**
Provides 1.0 mEq/L magnesium acetate when added to infusate.

- Magnesium Acetate: 13 g

**KCl**
Provides 1.0 mEq/L potassium chloride when added to infusate.

- Potassium Chloride: 9 g
Graph 2.3: Acetate Gain and Bicarbonate Loss
Graph 2.1: Patient Sodium vs Dialysate Sodium
Therapy Calculator

Data Input:
- Demographics: age, weight, gender, diabetes
- Monthly Labs: Na, HCO$_3^-$, BUN
- Disposables: dialyzer, cartridge choices
- Dialysate K, Ca, Mg.
- Blood flow rate, time of dialysis or dialysate flow rate

Output:
- Proper choice of column
- Length of dialysis or dialysate flow rate to produce 95% column saturation
- Dialysate NaHCO$_3$, NaCl, KCl packets required
On computer, entries and program operations were simple and became routine for each patient, but still required training...
Sorbent Cartridges Increased to Four (circa 2006-2007)

<table>
<thead>
<tr>
<th>Cartridge</th>
<th>Urea Load (g)</th>
<th>Therapy Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>SORB+</td>
<td>9.5 - 23.5</td>
<td>3:00 - 6:00</td>
</tr>
<tr>
<td>HISORB+</td>
<td>23.5 - 35.0</td>
<td>3:00 - 6:00</td>
</tr>
<tr>
<td>SORB HD</td>
<td>12.5 - 25.0</td>
<td>6:00 - 8:00</td>
</tr>
<tr>
<td>HISORB HD</td>
<td>15.0 - 30.0</td>
<td>6:00 - 8:00</td>
</tr>
</tbody>
</table>
## Changes in Sorbent Components of New Sorb Columns

<table>
<thead>
<tr>
<th>Component</th>
<th>Change</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Zirconium Phosphate</strong></td>
<td>Decreased pH, decreased sodium</td>
<td>Less Sodium release</td>
</tr>
<tr>
<td><strong>Charcoal</strong></td>
<td>Moved to First Layer</td>
<td>Improved water purification</td>
</tr>
<tr>
<td><strong>Zirconium Oxide</strong></td>
<td>Added Zirconium Carbonate</td>
<td>More bicarbonate, less pH decrease</td>
</tr>
<tr>
<td><strong>All of Above</strong></td>
<td>Increased Amount</td>
<td>Higher flow rates and clearances for longer duration</td>
</tr>
</tbody>
</table>
Based on expected dialysate BUN, column saturation was predictable...

\[ y = -0.0004x^3 + 0.0202x^2 + 0.3859x + 4.7186 \]

\[ R^2 = 0.9777 \]
Plasma sodium change was also predictable, but usually not avoidable...

Fig. 5. Plasma sodium change during treatment with a sorbent-based dialysis system, and comparison with changes predicted by the Prescription Guide.
By decreasing the pH of the ZP layer, sodium release was decreased to 10% of bound NH$_4^+$...
Changes in column effluent of bicarbonate were smoothed out..
Changes in pH were also smoothed out..
Treatments Were Successful; Allient System vs. Single Pass in Acute Environment

**URR Comparison**
- Total of 19 treatments with initial BUNs 40 – 60 at equivalent system settings
  - BFR = 300 ml/min
  - DFR = 400 ml/min
  - TT = 180 minutes

**Conclusion**
- As expected, comparable dialysis therapy effectiveness achieved with both systems when run at equivalent settings

Source: Acute Dialysis Facility

Technology: Update on Sorbent Therapy in the Hospital Setting
Amit Sharma, M.D., FACP, FASN
Director of Clinical Research
Boise Kidney & Hypertension Institute
What Happened to the Redy Machine and Sorb Column?

- Redy 2000 machine was never upgraded with controlled filtration, pure bicarbonate dialysis, ammonium monitor, etc.
- Dialysate flow was limited to 250 ml/min, not suiting rapid treatments being used for acute dialysis.
- Training nurses and doctors how to mix dialysate for each treatment, how to choose appropriate column and starting bath concentrations, how to monitor for ammonium, etc. became more and more difficult.
- Questions arose about aluminum toxicity, which only was a problem when citrate anticoagulation was used.

What Happened to the BioLogic-HD and Allient?

- BioLogic-HD was FDA approved to market in 1986, focus was on home dialysis. Months later CMS stopped payment for home helpers, market disappeared.
- Modified sorbents were then used in Liver Dialysis.
- Allient was FDA approved to market in 2006 for in-center patients.
- Clinical trials for home dialysis treatments progressed.
- Renal Solutions was purchased by FMC in 2007.
- FMC decided to re-design the machine and disposables to make the machine smaller and simpler to operate. Hasn’t happened yet (I think).
- Sorb column production was halted in 2014, but R&D continues (I think).
Zirconium Cyclo-Silicate (ZS-9)
A New Monovalent-Selective Cation Exchanger for Removing K\(^+\) and NH\(_4^+\)
ZS-9: A Novel Selective Potassium Trap

**Unique Properties**

- Not an organic polymer resin like SPS (Kayexalate®) or patiromer
- Designed and engineered to be selective for potassium
- Highly defined cubic lattice structure preferentially accommodates 3Å cations
- High thermal stability, non-swelling, non-absorbed inorganic crystal

**ZS-9 Crystal Structure**

Average binding site width 3Å
ZS-9 Pores/Windows Mimic Physiologic Ion Channel Selectivity

Hydrated Ion

ZS-9 Pore/Window

Energy to dehydrate the ion is more than balanced by the energy regained by the interaction with carbonyl oxygens.

Because Ca$^{2+}$ is too small to interact with the oxygens, entering the pore/window is energetically unfavorable.
Potassium Decline of 0.5 mEq/L in 12 Hours During Daytime Treatments with Oral ZS-9

Rate of Decline During Daytime Treatment Period
Serum Potassium (mEq/L)

<table>
<thead>
<tr>
<th>Mean Rate of Change (mEq/L/hr)</th>
<th>Placebo (N=30)</th>
<th>10g ZS-9 (N=24)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>“Treatment Period”</td>
<td>-0.011</td>
<td>-0.038</td>
<td><strong>0.001</strong></td>
</tr>
<tr>
<td>“Rebound Period”</td>
<td>0.010</td>
<td>0.024</td>
<td>0.166</td>
</tr>
</tbody>
</table>

ZS-9 was recently approved to market by FDA as an oral sorbent in treatment of hyperkalemia....
Mean Serum Calcium in CKD Patients on ZS-9 and Placebo

* Indicates significantly different compared with respective placebo group (p<0.05). Blue shading Indicates normal range.
Mean Serum BUN in CKD Patients on ZS-9 and Placebo

Blood Urea Nitrogen (mg/dL)

* Indicates significantly different compared with respective placebo group (p<0.05).
What if We Used ZS Instead of ZP in Dialysate Regeneration?

• Would need to create a structure to hold and evenly perfuse the small crystals (5-10 micron), like a carbon block
• Would not need Ca$^{++}$ and Mg$^{++}$ reinfusates
• Capacity for K$^{+}$ and NH$^{+}$ would approximately double (per gram)
• Cost would be high, but column could be regenerated with H$^{+}$ and Na$^{+}$ solution
Liquid Membrane Capsules for Binding NH3 (Gas-Permeable Membrane and Acid Trap)
Slow but effective binding of NH$_4^+$ 70 ml of LMC would bind 12 grams of urea.

Components: tartaric acid in mineral oil (with polymer and surfactant)
Recent Confirmation of “Acid Trap” Concept for Removal of NH$_4^+$

With a gas permeable membrane separating NH$_4^+$ solution from H$^+$-loaded cation exchanger, transfer of NH$_4^+$ is slow but capacity of sorbent is huge. Surrounding fluid pH drop is a problem.
What Happened to Liquid Membrane Capsules and the “Acid Trap” idea for Ammonium?

- Binding of NH$_4^+$ was slow but capacity high.
- Capsules were unstable, with coalescing when sitting still for a few minutes in the suspension.
- They were kind of messy.
- If capsules ruptured they would release acid into the gut.
- The concept is sound and with current membrane technology an “acid trap” may be a good addition to cation exchange layers to increase NH$_4^+$ binding capacity.
Calcium-Loaded Zeolites for Removal of NH$_4^+$
In the late 1970s we developed the world’s simplest hemodialysis system, with membranes acting as a blood pump to draw blood from a single access point. A suspension of sorbents surrounded the membranes. Urease catalyzed urea to ammonium and carbonate. Calcium-loaded synthetic zeolites (alumino-silicates) released calcium, which precipitated excess carbonate and also removed phosphate.
What happened to Calcium-Loaded Zeolites?

• Since the sorbent was a suspension, NH₄⁺ return to the patient was inescapable, though at tolerable levels in the body.
• In vitro and animal tests confirmed that the zeolites were not totally insoluble. Depending upon how they were constructed, either too much silica or too much alumina was released from the zeolites.
• Although there were technical solutions to solve this problem, they were deemed too expensive to continue the project.
Electro-oxidation of Urea
Electro-oxidation

Electro-oxidation means the use of electric fields in a fluid to induce oxidation of components such as urea. Surprisingly, this can be done safely in dialysate during hemodialysis.

\[
\begin{align*}
(NH_2)_2CO + H_2O & \rightarrow N_2 + CO_2 + 6H^+ + 6e^- \quad (1) \\
2Cl^- & \rightarrow Cl_2 + 2e^- \quad (2) \\
Cl_2 + H_2O & \rightarrow HOCl + HCl \quad (2) \\
(NH_2)_2CO + 3OCl^- & \rightarrow N_2 + CO_2 + 3Cl^- + 2H_2O \quad (2)
\end{align*}
\]

**FIG. 1.** Chemical equations involved in complete oxidation of urea during electro-oxidation of dialysate. Reaction 1: direct oxidation at the anode. Reaction(s) 2: indirect oxidation in the bulk solution. Oxidation of chloride ions at the anode yields chlorine gas. Chlorine gas reacts with water yielding hypochlorous acid (HOCl). Urea is oxidized by hypochlorite (OCl\(^-\)) (12.13).

**FIG. 2.** (A) Dialysis circuit in single pass configuration, consisting of two 3 L reservoirs, one pump (50 mL/min), and an electro-oxidation unit containing 10 electrodes. (B) Dialysis circuit in recirculation configuration, consisting of a 3 L reservoir, two pumps (speed of pump 1: 110 mL/min and of pump 2: 50 mL/min), a dialyzer, an EO unit, a degassing unit, and two AC filters in series, each containing 50 mL (25 g) AC.

*Maarten Wester, †Frank Simonis, ‡Nadia Lachkar, §Will K. Wodzig, ¶Frank J. Meuwissen, ††Jeroen P. Kooman, ‡‡Walther H. Boer, §§Jaap A. Joëls, and ¶¶Karin G. Gerritsen*
Problems with Electro-oxidation
Low Efficiency, Getting Rid of Chlorine

FIG. 4. Influence of dialysate urea concentration and current on urea removal rate and chlorine release. (A) Urea removal with increasing inlet concentration of urea at 3 A (left y-axis) and urea removal efficiency (mmol urea removed/mmol urea delivered per hour, right y-axis).
DKF is collaborating with the Utrecht scientists in further development of electro-oxidation.

**Removal of organic toxins by catalytic oxidation**

- Urea: 10-15 mmol/hr
- Creatinine: 0.6 mmol/hr
- Catalytic oxidation of urea: \( \text{CO(NH}_2\text{)}_2 + \text{H}_2\text{O} \rightarrow \text{N}_2 \uparrow + \text{CO}_2 \uparrow + 3\text{H}_2 \uparrow \)

**Graphs:**

- **Urea removal:** Blood hourly spiked with 10 mmol urea.
- **Creatinine removal:** Blood hourly spiked with 500 umol.

**After each hour toxins are spiked**
Role of Carbon in Removing Organic Uremic Toxins
Clearance of Uremic Markers is Very Low with Standard CVVHD

Figure 2
Time weighted average (TWA) clearance of (a) β2 microglobulin (beta2mic), (c) urea and (d) creatinine by convective and diffusive transport. (b) Beta2mic adsorptive clearance during continuous veno-venous hemofiltration (CVVH) and continuous veno-venous dialysis (CVVHD). Data are expressed as median and interquartile range. None of these comparisons reaches statistical significance.

Ave Qd = 2150 ml/hr, Ave Qb = 150 ml/min
Middle Molecule and Creatinine Clearances Increase with Dialysate Flow Rate During CVVHD

CVVHD clearance (ml/min) versus dialysate flow rate, blood flow 150-400 ml/min, no UF

Why be down here when you can be up here?
Charcoal absorbs about every organic compound over 100 m.w. and without high charge; almost every organic compound is bound better than creatinine.
Charcoal Has Selectivity for Many Organic Toxins; Example is Strong Affinity for Aromatic AA Vs. Branched Chain AA

**Charcoal Adsorption of Various Amino Acids**

In Vitro Studies with Individual Amino Acids

<table>
<thead>
<tr>
<th>Amino Acid</th>
<th>Mol Wt</th>
<th>Plasma Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenylalanine</td>
<td>165.2</td>
<td>165.2 mg/dl</td>
</tr>
<tr>
<td>Leucine</td>
<td>131.2</td>
<td>2</td>
</tr>
<tr>
<td>Glutamine</td>
<td>146.1</td>
<td>8</td>
</tr>
<tr>
<td>Valine</td>
<td>117.1</td>
<td>3</td>
</tr>
<tr>
<td>Alanine</td>
<td>89.1</td>
<td>3</td>
</tr>
</tbody>
</table>

**Graphical Representation:**

- **Bound Amino Acid (mg/g charcoal)** vs. **Unbound Amino Acid (mg/dl)**
- Different colors and symbols represent various amino acids.
- Phenylalanine shows strong affinity compared to other branched chain aminos.
Powdered Carbon Particles Work Better Than Granules, But Need to be Contained for Perfusion

- Sorbent Suspension Dialyzer (BioLogic-DT)
- Microfiber with embedded charcoal
- Filtration membranes with lots of shear
- Carbon Block
Carbon Block is Created by Mixing Powdered Carbon with Polyethylene and then Extruding as a Tube

Plastic spicules bind carbon particles together without masking the active surface area
Using a Carbon Block, Creating a Cartridge of Powdered Carbon with Even Flow Distribution is Easy, and Results Predictable
Middle Molecule Removal-PCS

OMB-934-1M Removal of p-Cresyl Sulfate

[Graph showing p-Cresyl sulfate removal over time with two curves, one for Tank 18 and one for Tank 19: Output, with a sharp decrease in concentration.]
Indoxyl Sulfate

Figure 2 – Results of Two Aqueous Experiments

OMB-934-1M Removal of Indoxyl Sulfate
Experiment 1, 1/29/18

OMB934-1M Removal of Indoxyl Sulfate
Experiment 2, 1/30/18

OMBS34-1M Adsorption of Indoxyl Sulfate
Beta-2 Microglobulin (WAK with Carbon Column)

Figure 7. Removal of \( \beta 2M \) from healthy human blood by WAK system is shown to be most effective in the first half-hour.

Technical Breakthroughs in the Wearable Artificial Kidney (WAK)

Victor Gura,*† Alexandra S. Macy,‡ Masoud Beizai,‡ Carlos Ezon,‡ and Thomas A. Golper§
*Cedars-Sinai Medical Center, Los Angeles, California; †UCLA Geffen School of Medicine, Los Angeles, California; ‡Xcorporal Inc., Los Angeles, California; §Vanderbilt University Medical Center, Nashville, Tennessee

Conclusions

- Carbon block columns effectively remove the most important toxins of uremia (organics, middle molecules)
- Carbon block column in a CVVHD circuit allows dialysate flow rate to be increased, improving clearance of organic toxins, and possibly improving clinical response
- Frequency of bag changes will determine clearance of small, charged uremic toxins
- Cost and effort of CVVHD will be diminished
- Other applications of CVVHD will be improved, including treatment of drug overdose, acute-on-chronic hepatic failure, hepato-renal failure, etc.
- Other powdered or granular sorbents may be combined with the carbon block in the future.
- Carbon block can effectively regenerate albumin solutions and plasma, so there may be applications in treatment of sepsis, immune diseases and hepatic failure (though bilirubin removal is slow)
- If there were an effective oral sorbent to bind many small and charged uremic toxins in the gut, then regenerating dialysate could be done by carbon alone, for HD and PD applications
Removal of Small or Charged Uremic Toxins Within the Gut
Clever Solution for Ion Removal from Water: Mixed Bed Deionizers\textsuperscript{[1950]}

Cations and anions are bound, counter-ions form \( \text{H}_2\text{O} \) and “disappear.” Result: Very high binding, pH unchanged.
So Why Not Use “Mixed Bed” Ion Exchange as an Oral Sorbent?

- Zirconium phosphate ($H^{+}$-ZP) as CATION exchanger (as in the Sorb™ column)
- Zirconium oxide ($OH^{-}$-ZO) as ANION exchanger (as in the Sorb™ column)
- Would bind $K^{+}$, $Na^{+}$, $HPO_{4}^{2-}$, $H^{+}$ and $NH_{4}^{+}$ (from urea)
- $H^{+}$ and $OH^{-} \rightarrow H_{2}O$, no counter-ions are released
- Some essential cations ($Mg^{++}$ and $Ca^{++}$) would be removed but could be replaced easily
- Surprisingly, this Mixed Sorbent appears to be a new idea!
Diagram of how Mixed Sorbent would work:

If the cation exchanger is non-selective, it will remove Mg\(^{++}\) and Ca\(^{++}\). Administering these cations replenishes Mg\(^{++}\) and Ca\(^{++}\) and also removes HPO\(_4\)^{--}. 
Test solutions simulated water of small bowel and colon with reported intestinal ion concentrations:

These solutions actually precipitated when created. Bicarbonate was therefore omitted during tests of H-ZP and H-ZP/OH-ZO.
Electrolyte Binding from SMALL BOWEL solution due to sorbents

Sorbent: Zirconium Phosphate-H (ZP) in 100 mL or ZP & Zirconium Oxide-OH (ZP&ZO) in 200 mL

NH₄ not included in small bowel solution
Electrolyte binding from simulated COLON solution due to sorbents
Sorbent: Zirconium Phosphate-H (ZP) in 100 mL or ZP & Zirconium Oxide-OH (ZP&ZO) in 200 mL

Amount bound, mEq/gram relevant sorbent

Electrolyte Exchanged

NH$_4^+$ Ca ++ Mg ++ K + Na + H + H$_2$PO$_4^-$ Cl-

- ZP
- ZP & ZO
Conclusions from Our In-Vitro Tests

- Standard inexpensive ion exchangers (H-ZP and OH-ZO) when taken orally will remove Na\(^+\), PO\(_4\)\(^-\), H\(^+\) and K\(^+\) very effectively from intestinal contents.
- Ca\(^{++}\) and Mg\(^{++}\) removal is modest and can be offset by administration of supplements orally.
- Binding of NH\(_4\)\(^+\) is much lower than desired, but could be higher in vivo than in vitro (as seen with ZS-9 in early clinical trials).
- 45 grams of this Mixed Sorbent in 3-4 ounces of water ingested daily would remove 100% of the total daily intake or generation of K\(^+\), PO\(_4\), Na\(^+\) and H\(^+\).
- Removal of 100% of urea nitrogen (at 10 meq NH\(_4\)\(^+\)/gram) would require an additional 70 grams of Mixed Sorbent.
CKD and ESRD Patients Already Ingest Multiple Sorbents to Bind Small, Charged Toxins

- For *phosphate*: calcium carbonate, calcium acetate, lanthanum carbonate, ferric citrate, sucroferric oxyhydroxide and sevelamer (*anion exchangers*)
- For *potassium*: sodium polystyrene sulfonate, calcium polystyrene sulfonate, patiromer and zirconium cyclosilicate (*cation exchangers*)
- For *acidosis*: sodium bicarbonate or sodium citrate (bind and remove H+)
- For *cholesterol*: cholestyramine (*anion exchanger*)
- For *sodium* and *urea*: no oral sorbent (yet), though urea and sodium are plentiful in the gut (50% of urea passes into the intestine daily, converts to ammonium and is resythesized to urea in the liver).
Maximum Daily Intake of Sorbents by CKD/ESRD patients

- Sevelamer: 14 grams (17.5 pills or 7.5 packets)
- Patiromer: 25 grams (one large packet)
- Sodium bicarbonate: 3 grams (5 pills) bb total: 42 grams

45 grams of ZP/ZO sorbent looks like this:
The Complexity of the Sorb™ Column for Dialysate Regeneration is Mostly Due to Removal of Small Charged Toxins

Fresh Dialysate

• Zirconium Oxide & Zirconium Carbonate Layer

• Zirconium Phosphate Layer

• Urease Layer

• Activated Carbon & Purification Layer

Binds:

- Phosphate
- Fluoride
- Heavy Metals
- Ammonium
- Calcium
- Magnesium
- Potassium
- Metals
- Other Cations
- Nothing (Converts Urea)
- Heavy Metals
- Oxidants
- Chloramine
- Creatinine
- Uric Acid
- Other Organics
- Middle Molecules

Releases:

- Acetate
- Bicarbonate
- Sodium
- Hydrogen

(Note: requires calcium and magnesium infusion after column)

Used Dialysate

This slide deck is for internal informational use only and is not for external use or discussion with customers.
If the Oral Sorbent Mixture is Effective, then All That is Needed is Charcoal to Regenerate Dialysate for HD or PD

Fresh Dialysate

- Zirconium Oxide & Zirconium Carbonate Layer
- Zirconium Phosphate Layer
- Urease Layer
- Activated Carbon & Purification Layer

Binds:
- Phosphate
- Fluoride
- Heavy Metals
- Ammonium
- Calcium
- Magnesium
- Potassium
- Metals
- Other Cations
- Nothing (Converts Urea)
- Heavy Metals
- Oxidants
- Chloramine
- Creatinine
- Uric Acid
- Other Organics
- Middle Molecules

Releases:
- Acetate
- Bicarbonate
- Sodium
- Hydrogen
- Ammonium Carbonate
- Nothing

(Note: requires calcium and magnesium infusion after column)
PD Therapy Made Simple, Safe and Highly Portable, Using Carbon Block to Regenerate Dialysate

UF

Flow-Through Catheters

Carbon Block

Glucose
HD Therapy Made Simple, Safe and Highly Portable, Using Carbon Block to Regenerate Dialysate
Five Obvious Questions About This New Therapy

1. Is there a mathematical model to predict chemical function of the mixed sorbents in a complex gut environment?
2. Do we have data to show that small, charged uremic toxins can be sufficiently removed from the gut to normalize or stabilize serum levels of the toxins?
3. How did we calculate the amount of ZP/ZO mixture needed for maximal effect on the toxins?
4. Will zirconium be solubilized and absorbed from the gut?
5. Will this cause any problems in the patients?
Five Short Answers

1. Is there a mathematical model to predict chemical function of the mixed sorbents in a complex gut environment? *Yes, it gives rough estimates*

2. Do we have data to show that small, charged uremic toxins can be sufficiently removed from the gut to normalize or stabilize serum levels of the toxins? *Yes*

3. How did we calculate the amount of ZP/ZO mixture needed for maximal effect on the toxins? *From in vitro studies and daily generation of toxins*

4. Will zirconium be solubilized and absorbed from the gut? *Yes*

5. Will this likely cause any problems in the patients? *No*
Thanks for Your Attention and Your Vision of the Future