Glucose Sparing Strategies

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Glucose Sparing Strategies

Why?

• Glucose is still the best osmotic agent we have!
• There is no alternative agent that can replace glucose!
• Glucose fits “almost” the definition of an ideal osmotic agent
  — Bodily ingredient
  — Easily metabolized
  — Not retained in the body
  — No major systemic toxicities
  — Metabolic problems
*Nephron* 1986;42:93-101

- “glucose will remain the osmotic agent for PD for the foreseeable future”

- Therefore, effort should be made to optimize the amount of glucose used to achieve adequate UF

**Systemic Effects: Glucose or GDPs in PD**

- lipid changes, and consequently cardiovascular events and endocrine changes
- hyperglycemia and associated hyperinsulinemia in both diabetic as well as nondiabetic patients
- an increase in total fat mass and increased fat accumulation
- compared with polyglucose PD solution, use of 3.6% glucose solutions have been shown to cause increased BP along with higher heart rate, stroke volume, and cardiac output
Effects on Mesothelial Cells

- Both animal and human observations indicate that glucose *per se or in hypertonic concentrations along with its degradation product in an acidic pH are detrimental to mesothelial cell function, viability, and life cycle over longterm PD

The extent of glucose absorption

- for a 6-h dwell of a 2 l PD solution:
  - 1.5% solution: 15–22 g
  - 2.5% solution: 24–40 g
  - 4.25%: 46–60 g
- per day:
  - Approximately absorbed range of 100–300 g for CAPD patients
- per year:
  - Approximately 40 to over 100 kg
UF EFFICIENCY

- Defined as the amount of net UF obtained for every gram of carbohydrate absorbed
- UF efficiency index will vary:
  - between patients
  - and is affected by the conditions of the dwell
  - Transport type

Short Dwell Studies

© Holmes and S Muijs: Glucose sparing in PD

Figure 2 | Net UF during a PET with 2.5% dextrose displayed by PET categories. L = low transport; LA = low-average transport; HA = high-average transport; H = high transport.
Figure 3 | Glucose absorption during a PET with 2.5% dextrose displayed by PET categories. L = low transport; LA = low-average transport; HA = high-average transport; H = high transport.

Figure 4 | UF efficiency during a PET with 2.5% dextrose displayed by PET categories. L = low transport; LA = low-average transport; HA = high-average transport; H = high transport.
Long Dwell Evaluation
UF Efficiency in CAPD

- UF efficiency during the long dwell of CAPD in 94 patients studied with 2.5% dextrose and then re-evaluated with the alternate osmotic agent polyglucose
Figure 1 | Mathematical modeling of glucose absorption in CAPD patients with various membrane transport characteristics. The model assumes three short dwells of 5 h and a long dwell of 9 h. Legend: L = low (MTAC 5.96 ml/min); LA = low-average (MTAC 8.33 ml/min); HA = high-average (MTAC 11.7 ml/min); H = high (MTAC 16.3 ml/min).

Table 3 | Comparison of icodextrin and 2.5% dextrose during the long dwell in CAPD patients

<table>
<thead>
<tr>
<th></th>
<th>Dwell time (h)</th>
<th>Net UF (ml)</th>
<th>CHO absorbed (g)</th>
<th>UF efficiency (ml/g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.5% Dextrose</td>
<td>10.1 ± 0.1</td>
<td>271 ± 42</td>
<td>39.3 ± 0.7</td>
<td>7.9 ± 1.3</td>
</tr>
<tr>
<td>Icodextrin</td>
<td>10.6 ± 0.1</td>
<td>599 ± 33</td>
<td>34.6 ± 2.0</td>
<td>27.8 ± 3.3</td>
</tr>
<tr>
<td>P-value</td>
<td>0.001</td>
<td>&lt;0.0001</td>
<td>&lt;0.05</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

CAPD, continuous ambulatory peritoneal dialysis; CHO, carbohydrate; UF, ultrafiltration. Values are mean ± s.e.

Table 4 | Comparison of icodextrin and 4.25% dextrose during the long dwell in APD patients

<table>
<thead>
<tr>
<th></th>
<th>Dwell time (h)</th>
<th>Net UF (ml)</th>
<th>CHO absorbed (g)</th>
<th>UF efficiency (ml/g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.25% Dextrose</td>
<td>14.2 ± 0.1</td>
<td>220 ± 86</td>
<td>77.7 ± 1.4</td>
<td>3.1 ± 1.1</td>
</tr>
<tr>
<td>Icodextrin</td>
<td>14.1 ± 0.1</td>
<td>540 ± 46</td>
<td>56.2 ± 2.4</td>
<td>10.9 ± 1.1</td>
</tr>
<tr>
<td>P-value</td>
<td>0.64</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

APD, automated peritoneal dialysis; CHO, carbohydrate; UF, ultrafiltration. Values are mean ± s.e.
summary of more recent clinical observations

- In both diabetics and non-diabetics - use of non-glucose during a long dwell achieves a reduction in total carbohydrate absorption while maintaining adequate UF
- Potential for improving insulin sensitivity
- In diabetic patients - improved glycemic control & reduced hemoglobin (Hb) A1c
- Beneficial changes in plasma adipokine levels, glucose and lipid oxidation, and systemic hemodynamic effects
- Experience to date is promising
- A need for further studies to confirm and to extend these observations

Table 5 | A summary of demonstrated and emerging clinical benefits of glucose-sparing approaches

<table>
<thead>
<tr>
<th>Patient population</th>
<th>Prescription</th>
<th>Observations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-diabetic CAPD</td>
<td>Icodextrin vs glucose</td>
<td>Decreased serum insulin (HOMA)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Improved insulin sensitivity (HOMA)</td>
</tr>
<tr>
<td>Non-diabetic CAPD</td>
<td>Icodextrin vs glucose</td>
<td>Decreased plasma total cholesterol</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Decreased LDL</td>
</tr>
<tr>
<td>Diabetic</td>
<td>Icodextrin vs glucose</td>
<td>HbA1c decreased with icodextrin use (8.0±0.7 to 7.1±0.4; P&lt;0.05)</td>
</tr>
<tr>
<td>CAPD with hypertriglyceridemia</td>
<td>Icodextrin vs glucose</td>
<td>Significant fall in triglycerides in icodextrin group</td>
</tr>
<tr>
<td>All PD</td>
<td>Icodextrin vs glucose</td>
<td>Gastric emptying time significantly shorter with icodextrin group</td>
</tr>
<tr>
<td>All PD</td>
<td>Icodextrin vs glucose</td>
<td>No increase in non-fluid weight gain in icodextrin group unlike glucose group</td>
</tr>
<tr>
<td>Diabetic CAPD</td>
<td>Icodextrin, amino acids and glucose vs all glucose</td>
<td>Significantly improved glycemic control</td>
</tr>
<tr>
<td>All PD</td>
<td>Icodextrin and amino acids vs glucose</td>
<td>Improved glucose and lipid metabolism (increased oxidation, decreased lipid oxidation)</td>
</tr>
<tr>
<td>CAPD</td>
<td>Icodextrin vs 3.86% glucose</td>
<td>Increased heart rate, stroke volume and thus cardiac output, leading to increased blood pressure during dwell glucose vs icodextrin</td>
</tr>
<tr>
<td>Non-diabetic</td>
<td>Icodextrin vs glucose</td>
<td>Decreased plasma leptin, insulin and triglycerides in icodextrin group</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Increased adiponectin and HDL, and improved insulin sensitivity (HOMA) in icodextrin group</td>
</tr>
</tbody>
</table>

CAPD, continuous ambulatory peritoneal dialysis; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; HOMA, Homeostatic Model Assessment.

Holmes and S Muir: Glucose sparing in PD
Glucose sparing Strategies

Prescriptions

• Reduce the need for ultrafiltration:
  – (a) Dietary salt and water restriction
  – (b) Use of diuretics with RRF
  – (c) Preserve residual GFR

• 2. Optimization of peritoneal ultrafiltration with minimization of glucose use

• Use solutions with high UF efficiency with glucose
  – (a) Use PD solutions with colloidal osmotic agent for the long dwell
  – (b) Use of amino-acids-based solution in short dwells
  – (c) Use combination of colloidal and crystalloid solutions

• Use low GDP solutions

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Table 2. Change from baseline and between-group differences for a variety of criteria according to treatment group

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Month 1</th>
<th>Month 3</th>
<th>Month 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urine volume (ml)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Icodextrin</td>
<td>-44.3</td>
<td>-34.6</td>
<td>-10.7</td>
</tr>
<tr>
<td>Control</td>
<td>-44.1</td>
<td>-56.6</td>
<td>-126.6</td>
</tr>
<tr>
<td>Difference</td>
<td>-0.2</td>
<td>21.9</td>
<td>115.9*</td>
</tr>
<tr>
<td>Ultrafiltration volume (ml)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Icodextrin</td>
<td>+166.8</td>
<td>+87.9</td>
<td>+193.4</td>
</tr>
<tr>
<td>Control</td>
<td>-50.1</td>
<td>-311.1</td>
<td>-201.7</td>
</tr>
<tr>
<td>Difference</td>
<td>210.9</td>
<td>399.0*</td>
<td>395.1</td>
</tr>
<tr>
<td>Total fluid loss (ml)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Icodextrin</td>
<td>+138.8</td>
<td>+66.0</td>
<td>+258.6</td>
</tr>
<tr>
<td>Control</td>
<td>-37.2</td>
<td>-307.8</td>
<td>-141.8</td>
</tr>
<tr>
<td>Difference</td>
<td>176.0</td>
<td>373.8*</td>
<td>400.4</td>
</tr>
<tr>
<td>Dialysate sodium loss (mmol)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Icodextrin</td>
<td>+11.5</td>
<td>+4.9</td>
<td>+1.4</td>
</tr>
<tr>
<td>Control</td>
<td>-11.4</td>
<td>-60.8</td>
<td>-23.0</td>
</tr>
<tr>
<td>Difference</td>
<td>22.9</td>
<td>61.7*</td>
<td>24.5</td>
</tr>
<tr>
<td>Total sodium loss (mmol)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Icodextrin</td>
<td>+8.3</td>
<td>+4.3</td>
<td>+5.4</td>
</tr>
<tr>
<td>Control</td>
<td>2.4</td>
<td>-33.0</td>
<td>-39.9</td>
</tr>
<tr>
<td>Difference</td>
<td>5.9</td>
<td>37.3*</td>
<td>25.2</td>
</tr>
</tbody>
</table>

Figure 2. Changes in (a) drained body weight and (b) total body water determined from deuterium dilution. At each time point, values represent mean ± SEM change from baseline for patients randomized to icodextrin (□) or 2.27% glucose (■). Between-group differences, †P < 0.05, ‡P < 0.04. Longitudinal differences from baseline, *P < 0.04. **P < 0.001.
further analysis:
Answer questions

• (i) Is there a relationship between changing fluid status and urine volume and if so, was this the same for glucose and icodextrin?


Fig. 1. Relationship between the change in ECFv and urine volume observed at (a) 3 months and (b) 6 months post-randomization. Data are shown separately for the icodextrin treated (•, solid regression line) and glucose 2.27% (□, dashed regression line). At both time points for both solutions, there was a significant negative relationship (see the text for details). The relative reduction in urine volume for a given fall in ECFv appears less in the icodextrin group.
Conclusions

- Polyglucose substituted for glucose as the osmotic agent in dialysate for the long dwell exchange provides:
  - sustained ultrafiltration (UF) through colloid osmosis
  - reduce exposure to and absorption of glucose, along with a consistent reduction in extracellular fluid volume without the expected fall in urine output
Concerns

• Icodextrin, one exchange/day is not sufficient to achieve adequate fluid balance in many patients without resorting to hypertonic glucose during the daytime exchanges in CAPD or the overnight APD session and/or
• Without reducing fluid and sodium intake, using 7.5% icodextrin may not achieve the required fluid and sodium balance in a number of anuric or fluid overloaded patients

Practical Solutions

• Reduction of peritoneal glucose load using commercially available amino acid or icodextrin PD solutions in combination with glucose-based PD solutions during overnight APD
• Induce crystalloid and colloid osmosis based on mixing a small molecular component (glucose or amino acids) with a glucose polymer formulations ranging from 2% to 7.5% during a long dwell exchange
Preliminary Observations

• compared to using polyglucose solutions during a 15-hour dwell in APD patients mixtures achieve approximately
  – Double net UF
  – triple sodium removal

  – Freida P, Galach M, Divino Filho JC, Werynski A, Lindholm B. Combination of crystalloid (glucose) and colloid (icodextrin) osmotic agents markedly enhances peritoneal fluid and solute transport during the long PD dwell. Perit Dial Int 2007; 27:267–76
  – Jenkins SB, Wilkie ME. An exploratory study of a novel peritoneal combination dialysate (1.36% glucose/7.5% icodextrin), demonstrating improved ultrafiltration compared to either component studied alone. Perit Dial Int 2003; 23:475–80

Study Design

• A 2 parallel arm, 4 month, prospective nonrandomized study

Objectives

• patients on automated PD (APD)
• fast transport patients
• Assess glucose-sparing advantage between 7.5% polyglucose solution during long dwell (15 hours) with a mixed crystalloid and colloid PD fluid
• Daytime UF and sodium removal while diminishing the glucose strength at night

dual osmotic solution

• prepared by mixing 200 mL 30% glucose (MacoPharma, Tourcoing, France) with 2.1 L (bag overfill) 7.5% polyglucose:
  – Na - 121 mEq/L
  – Glucose 2.61%
  – icodextrin concentrations 6.8%
  – the calculated osmolarity - 412 mOsm/L
Mixing solutions

Figure 1 — Study design. ICOD = icodextrin; UF = ultrafiltration; M1/M4 = month 1/4.
Results

- During the 4-month intervention period, net UF and peritoneal sodium removal during the long dwell when treated by bimodal UF was about 2-fold higher than baseline (with ICO).
- The estimated percent change from baseline in net daytime (longdwell) UF for the bimodal solution was 150% versus 18% for ICO (p < 0.001).
- The estimated percent change from baseline in peritoneal sodium removal for the bimodal solution was 147% versus 23% for ICO (p < 0.001).
- The estimated percent change from baseline in UF efficiency (24-hour net UF divided by the amount of glucose absorbed) was significantly higher (p < 0.001) when using the bimodal solution; 71%, versus –5% for ICO.
Summary

- Due to its capacity to achieve most of the required fluid and sodium removal during the long dwell exchange, bimodal ultrafiltration might be confirmed as a powerful glucose-sparing strategy for volume control in high-transport APD patients.

Concerns

- Potential metabolic concerns:
  - a relative hyponatremia
  - occasional case reports where patients have become unwell
  - cautions around the use of two icodextrin exchanges per 24 hours that would need to be addressed through further detailed study.
  - Icodextrin is generally priced higher than glucose based solutions.
MIXES WITH AMINO ACIDS

• The potential advantages of mixing glucose with amino acid solutions:
  – reduced glucose exposure
  – nutritional benefit
• Mixing icodextrin with amino acids in the same dialysate for glucose:
  – No need of glucose
  – Food value
  – Crystalloid and colloidal osmotic effect
  – mixed separately with icodextrin, glycerol, and glucose

A RANDOMIZED CLINICAL TRIAL WITH A 0.6% AMINO ACID/1.4% GLYCEROL PERITONEAL DIALYSIS SOLUTION

• solution is safe and well tolerated
• Glucose load was reduced significantly
• dialysate CA125 levels improved significantly.
• Ultrafiltration was comparable with that of a 2.27% glucose solution.
• potential nutritional benefits

Summary

Glucose Sparing Recommendations

- in patients who do not have UF difficulties:
  - Use icodextrin combined with amino acids as part of the APD prescription in order to reduce glucose exposure
  - reservations about recommending two icodextrin exchanges in 24 hours until there is a better understanding about the safety of this approach
- UF failure: combination solutions with icodextrin and glucose for the long dwell - increments in sodium removal and UF
- Another approach - combine reduction in glucose exposure through using amino acid, (overnight APD prescription), and use of polyglucose as part of a bimodal solution for the long daytime dwell