SODIUM GLUCOSE CO-TRANSPORTER 2 (SGLT2) INHIBITORS
A Novel Class of Antidiabetic Agents

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Upon completion of this presentation, the learner should be able to:
1. Recall the mechanism of action of the SGLT2 Inhibitors
2. Identify patients who may benefit from this class of medications based on proposed clinical advantages
3. Assess the available evidence on the safety and efficacy of this class of medications

History of Antidiabetic Medications

<table>
<thead>
<tr>
<th>Pharmacologic Agent</th>
<th>Year of FDA-Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Humulin R, HumulinH</td>
<td>1982</td>
</tr>
<tr>
<td>Glipizide</td>
<td>1984</td>
</tr>
<tr>
<td>Metformin</td>
<td>1994</td>
</tr>
<tr>
<td>Acarbose</td>
<td>1995</td>
</tr>
<tr>
<td>Actos® (pioglitazone)</td>
<td>1999</td>
</tr>
<tr>
<td>Byetta® (exenatide)</td>
<td>2005</td>
</tr>
<tr>
<td>Januvia™ (sitagliptin)</td>
<td>2006</td>
</tr>
</tbody>
</table>

Adapted from http://online.factsandcomparisons.com

Discovery of SGLT2 Inhibitors

- Phlorizin
  - First isolated in 1835 from root bark of apple tree
  - Effective in lowering both fasting blood glucose (FBG) and postprandial blood glucose (PPBG) in animal models
  - Not developed as a drug due to adverse effects and metabolism issues

Sodium Glucose Co-Transporters

<table>
<thead>
<tr>
<th>Gene</th>
<th>Protein</th>
<th>Substrates</th>
<th>Tissue Distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>SLC5A1</td>
<td>SGLT1</td>
<td>Glucose, galactose</td>
<td>SI, heart, trachea, kidney</td>
</tr>
<tr>
<td>SLC5A2</td>
<td>SGLT2</td>
<td>Glucose</td>
<td>Kidney</td>
</tr>
<tr>
<td>SLC5A4</td>
<td>SGLT3</td>
<td>Glucose sensor</td>
<td>SI, uterus, lungs, thyroid, testis</td>
</tr>
<tr>
<td>SLC5A9</td>
<td>SGLT4</td>
<td>Mannose, glucose, fructose, 1,3-AG, galactose</td>
<td>SI, kidney, liver, stomach, lung</td>
</tr>
<tr>
<td>SLC5A10</td>
<td>SGLT5</td>
<td>Glucose, galactose</td>
<td>Kidney</td>
</tr>
<tr>
<td>SLC5A11</td>
<td>SGLT6</td>
<td>Myo-inositol, glucose, xylose, chiro-inositol</td>
<td>Spinal cord, kidney, brain, SI</td>
</tr>
</tbody>
</table>

1,3-AG:1,3-anhydro-d-glucitol; SLC: solute carrier family; SI: small intestine


Sodium Glucose Co-Transporter 2 (SGLT2)

- Located in the proximal convoluted tubule
- Primary mediator of renal glucose reabsorption

http://kidney.niddk.nih.gov
Sodium Glucose Co-Transporter 2 (SGLT2) Con’t...

Mechanism of SGLT2 Inhibitors

Inhibit the renal reabsorption of glucose, thus increasing urinary glucose excretion and lowering plasma glucose levels

Potential Clinical Advantages

1. May improve both FBG and PPBG
2. Synergistic effects with other antidiabetic agents
   - May be beneficial for patients with type 1 diabetes
3. No hypoglycemia
   - Does not induce insulin secretion or inhibit hepatic glucose production
   - If blood glucose is low, renal filtration does not occur
4. Weight loss
   - Advantage over insulin, sulfonylureas, and TZDs
5. No gastrointestinal adverse effects
   - Advantage over metformin
6. Osmotic diuretic effect
   - Advantage in patients with CHF

Potential Clinical Disadvantages

1. Adverse effects secondary to glycosuria
   - Increased risk of urinary tract infection
   - Increased risk of bacterial/fungal vaginitis

Dapagliflozin

- Once-daily oral antidiabetic agent
- Longer half-life and duration of action than phlorizin
- Less adverse effects due to selectivity for SGLT2
- Manufactured by Bristol-Myers Squibb and AstraZeneca
Dapagliflozin: Preliminary study

- Doses of 0.01-1.0 mg/kg/day provided to diabetic rats for 15 days led to significant decreases in FBG and PPBG

Dapagliflozin: Phase IIa Study

- Four treatment groups:
  1. Placebo (n=8)
  2. Dapagliflozin 5mg/day (n=11)
  3. Dapagliflozin 25mg/day (n=12)
  4. Dapagliflozin 100mg/day (n=16)

Baseline Characteristics of All Patients (N=47)

- Established type 2 Diabetes
- Age 18 – 77 years
- Drug naïve or on stable dosage of metformin for ≥ 4 weeks
- Hemoglobin A1C 6-10%
- FBG ≤ 240 mg/dL

Phase IIa Study Con’t...

24-Hour Urinary Glucose Excretion

- Mean Cumulative Urinary Glucose (gm/day)

- Dapagliflozin (mg/day)

- Placebo 5 25 100

- Day 1 14

- * P < 0.05

Adapted from Fonseca VA, American Association of Clinical Endocrinology

Phase IIa Study Con’t...Change in Blood Glucose

- Placebo 5 25 100

- FBG at Day 13 14

- * P < 0.05

Adapted from Fonseca VA, American Association of Clinical Endocrinology

Phase IIa Study Con’t...Safety Endpoints

- No discontinuations due to adverse events
- Most common adverse events: constipation, nausea, and diarrhea
  - Three of 7 who experienced constipation received dapagliflozin alone
- Other adverse events:
  - Hypoglycemia: 2 patients
    - Both received dapagliflozin + metformin
  - Vaginovaginal infection: 2 patients
    - One received dapagliflozin alone, one received dapagliflozin + metformin

Phase IIa Study Con’t...Other Findings

- Urine volume and frequency
  - No change
  - No polyuria or nocturia
- Electrolytes
  - Changes in urinary Na+ excretion from Day -2 to Day 13
    - Placebo group: increased by + 5 mEq (±27)
    - Dapagliflozin 100mg group: increased by + 10 mEq (±67)
  - No change in other urine or plasma electrolytes
### Ongoing Clinical Trials

<table>
<thead>
<tr>
<th>Phase</th>
<th>Study Description</th>
<th>Study Design</th>
<th>Start Date</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>III</td>
<td>Efficacy and safety of dapagliflozin in patients uncontrolled on metformin alone</td>
<td>Randomized, double-blind, parallel group</td>
<td>September 2007</td>
<td>November 2008</td>
</tr>
<tr>
<td>III</td>
<td>Dapagliflozin in patients uncontrolled with diet and exercise alone</td>
<td>Randomized, double-blind, parallel group</td>
<td>September 2007</td>
<td>February 2009</td>
</tr>
<tr>
<td>III</td>
<td>Efficacy and safety of dapagliflozin in combination with metformin IR</td>
<td>Randomized, double-blind, active-control, parallel group</td>
<td>March 2008</td>
<td>August 2009</td>
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<tr>
<td>III</td>
<td>Efficacy and safety of dapagliflozin in combination with metformin</td>
<td>Randomized, double-blind, parallel group</td>
<td>March 2008</td>
<td>February 2011</td>
</tr>
<tr>
<td>III</td>
<td>Efficacy and safety of dapagliflozin in patients uncontrolled on insulin alone</td>
<td>Randomized, double-blind, parallel group</td>
<td>April 2008</td>
<td>March 2010</td>
</tr>
</tbody>
</table>

### Other SGLT2 Inhibitors in Development

- **Sergliflozin**
  - Three phase II studies in humans completed
    - Very small number of participants (n=18, 14, and 8)
    - Results indicated possible association with weight loss and transient changes in urine electrolytes

- **Remogliflozin**
  - One phase I study in humans completed (n=48)
    - No data available at this time

### References

7. Laffel L, Frier B, Pajvani UF, et al. Dapagliflozin and Sergliflozin increase the urinary excretion of glucose by selectively inhibiting the sodium-glucose co-transporter type 2 that is found on the renal proximal tubule.
8. May be useful in patients with type 2 or 1 diabetes
   - FDA-approval being sought for patients with type 2 diabetes
9. Monotherapy or in combination with other agents
   - Degree of effect on Hemoglobin A1C uncertain
10. Data from pharmacokinetic studies has confirmed that Dapagliflozin is safe in patients with renal impairment.