Five Things Your Patients With Diabetes May Ask You About

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September 12, 2015
Presenter Disclosure

• Presenter’s Name: Rhonda Roedler

• I have no current or past relationships with commercial entities

• Speaking Fees for current program:
  – I have received no speaker’s fee for this learning activity
Commercial Support Disclosure

• This program has received no financial or in-kind support from any commercial or other organization
Learning Objectives

• To learn about some of the latest developments affecting diabetes
  – Diabetes vaccine
  – Insulin pump
  – Bionic Pancreas
  – Cardiovascular outcomes with DPP-4 inhibitors
  – SGLT-2 and diabetic ketoacidosis
One Friday Morning.....

Accessed June 19, 2015
Effects of High-dose Oral Insulin on Immune Responses in Children at High Risk for Type 1 Diabetes

JAMA 2015;313(15):1541-1549
Background\textsuperscript{1,2}

- Proteins often the trigger for immune responses
- Antigen specific therapies have been successful with allergy and multiple sclerosis
- Type 1 Diabetes autoimmune disease
- Oral administration of insulin reduces development of diabetes in animals
- Induction of insulin-specific regulatory T cells
Pre-POINT Trial

P: Age 2-7, sero-negative for autoantibodies for insulin, GAD65 and IA-2 and high risk for developing Type 1 diabetes

I: Increasing dose of insulin in capsules depending on study block

GAD65 – major pancreatic islet cell antibody and marker of predisposition to Type 1 diabetes
IA2 – antibody against islet cell present at diagnosis of type 1 diabetes or suggesting a high risk for diabetes\(^3\)
2.5 mg insulin for 6 months

7.5 mg for 3-12 months

22.5 mg for 3-12 months

7.5 mg for 6 months

67.5 mg for 3-12 months

22.5 mg for 3-12 months

67.5 mg 3-12 months
Pre-POINT

E: 1° : positive immune response to insulin
   ↑ IgG antibodies to insulin
   ↑ salivary IgA antibodies to insulin
   ↑ CD4+ T-cell response to insulin

2° : gene expression profile of CD4+ cells responding to insulin

Adverse events
Results

• 33 children eligible
• Based on:
  • HLA DRB1-DQA1-DQB1 genotype
  • Lack of antibodies to GAD65 and IA-2
Results

• No reports of hypoglycemia
• No development of autoantibodies to GAD65 or IA-2
• No allergic reactions
Table 3. Immune Responses to Insulin According to the Study Drug and Dose Received at the Time of the Response

<table>
<thead>
<tr>
<th>Immune Response to Insulin</th>
<th>Placebo 2.5</th>
<th>Placebo 7.5</th>
<th>Placebo 22.5</th>
<th>Placebo 67.5</th>
<th>Insulin, mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum IgG</td>
<td>1/10 (10)</td>
<td>0/6 (0)</td>
<td>1/6 (17)</td>
<td>3/6 (50)</td>
<td>0.09 (0.0-0.46)</td>
</tr>
<tr>
<td>Salivary IgA</td>
<td>0/10 (0)</td>
<td>0/6 (0)</td>
<td>0/6 (0)</td>
<td>0/6 (0)</td>
<td>0.09 (0.0-0.46)</td>
</tr>
<tr>
<td>CD4+ T cells</td>
<td>1/7 (14)</td>
<td>1/6 (17)</td>
<td>0/5 (0)</td>
<td>1/5 (20)</td>
<td>0.09 (0.0-0.46)</td>
</tr>
<tr>
<td>Antibody or CD4+ T-cell response</td>
<td>2/10 (20)</td>
<td>1/6 (17)</td>
<td>2/6 (33)</td>
<td>5/6 (83)</td>
<td>0.09 (0.0-0.46)</td>
</tr>
</tbody>
</table>

Footnotes:
1. Responses are assigned according to the insulin dose at first observation.
2. From χ² test for trend.
3. A positive response for serum IgG binding to insulin was defined as a change from baseline of more than 10 counts per minute.
4. A positive salivary IgA response to insulin was defined as an increase of more than 5 SDs from the mean counts per minute of 10 asymptomatic antibody-negative children.
5. A positive CD4+ T-cell response to insulin was defined as a stimulation index of 3 or greater and a 2-fold or greater increase in the stimulation index over the baseline value.

Table 3: Effects of High-Dose Oral Insulin on Immune Responses in Children at High Risk for Type 1 Diabetes: The Pre-POINT Randomized Clinical Trial.

Bonifacio, Ezio; Ziegler, Anette-G; Klingensmith, Georgeanna; Schober, Edith; Bingley, Polly; Rottenkolber, Marietta; Theil, Anke; Eugster, Anne; Puff, Ramona; Peplow, Claudia; Buettner, Florian; Lange, Karin; Hasford, Jorg; Achenbach, Peter

DOI: 10.1001/jama.2015.2928
What This Tells Us

• Daily oral administration of 67.5 mg of insulin resulted in an immune response without hypoglycemia

• Promising results that those at high risk may not develop Type 1 diabetes
What This Doesn’t Tell Us

• Will it actually prevent Type 1 diabetes from occurring in the long term?
• Does it delay the onset of diabetes?

Phase 3 trials are currently underway, results are expected in 2017
COMPARISON BETWEEN MULTIPLE DAILY INSULIN INJECTION THERAPY (MDI) AND CONTINUOUS SUBCUTANEOUS INSULIN INFUSION THERAPY (CSII)
RESULTS OF THE FIVE NATIONS STUDY
Background\textsuperscript{4,5}

- Importance of intensive control of diabetes demonstrated by DCCT and UKPDS
- Options for control using multiple daily injections or continuous subcutaneous insulin infusion
- Objective to compare CSII to MDI with respect to metabolic parameters
Criteria for Starting Pump Therapy

1. Resident of Alberta and eligible for Alberta Health Care
2. Have type 1 diabetes
3. Testing blood glucose four times daily for at least 1 month
4. Last 2 consecutive A1c values 9.0% or less
5. Completed Pre-pump Information Session
6. Had at least 1 appt in the past year with a diabetes specialist or diabetes health provider
7. Adequate carbohydrate counting skills
8. Demonstrated understanding of and ability to adjust food, activity and insulin to prevent hypo and hyperglycemia.
What is Covered?

- Insulin pump every five years;
- Infusion sets: up to 100 units per 100 days;
- Insulin cartridges / reservoirs: up to 100 units per 100 days;
- Serters: up to 1 unit per year;
- IPT skin preparation (dressings and/or skin adhesives and/or adhesive removers): up to $100 per year;
- Blood glucose test strips: up to 700 units per 100 days;
- Blood ketone test strips: up to 20 units per 100 days;
- Blood ketone test meter: up to 1 unit every 2 years;
- Lancets: up to 700 units per 100 days; and
- Insulin syringes or pen tip needles: up to 100 units per 100 days.
Why use an insulin pump?\textsuperscript{4,5}

- Insulin absorbed more efficiently and predictably
- May reduce large fluctuations in blood glucose levels
- Improve blood glucose control
- Increase flexibility and timing of meals
- Decrease risk of hypoglycemia during exercise
- Improve quality of life

- Ideal for those with:
  - Hypoglycemia unawareness
  - Severe and frequent hypoglycemia
  - Frequent nocturnal hypoglycemia
  - Gastroparesis
  - Unpredictable lifestyle
  - Extreme insulin sensitivity
  - Dawn phenomenon
  - Planning for/during pregnancy
http://www.animas.ca/animas-insulin-pumps/animas-vibe
http://www.animas.ca/animas-insulin-pumps/onetouch-ping-insulin-pump
http://www.myomnipod.ca
https://www.medtronicdiabetes.ca/
https://www.accu-chekinsulinpumps.com/ipus/
Dosage instructions are entered into the pump's small computer and the appropriate amount of insulin is then injected into the body in a calculated, controlled manner.

CSII vs MDI

- 272 individuals enrolled and 223 completed the study
- Insulin lispro used as mealtime insulin in both CSII and MDI
- NPH insulin used as basal insulin within MDI group
Results

<table>
<thead>
<tr>
<th>Parameter</th>
<th>MDI</th>
<th>CSII</th>
<th>Statistical Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1c</td>
<td>7.67%</td>
<td>7.45%</td>
<td>Non-inferior*</td>
</tr>
<tr>
<td>Hypoglycemia (mild)</td>
<td>85.7 events/pt year</td>
<td>79.3 events/pt year</td>
<td>p=0.057</td>
</tr>
<tr>
<td>Hypoglycemia (severe)</td>
<td>0.5 events/pt year</td>
<td>0.2 events/pt year</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>DQoL score</td>
<td>71</td>
<td>75</td>
<td>p&lt;0.001</td>
</tr>
</tbody>
</table>
What does this tell us?

- Shows at least non-inferiority of CSII over NPH
- Improvement in rates of hypoglycemia
- Improvement in patient satisfaction
- No difference in rates of DKA
What does this study not tell us?

• Is it any better than basal analogue based MDI regimens?
• No long term data to determine if benefits continue
American Association of Clinical Endocrinologists (AACE)
24th Annual Scientific and Clinical Congress
May 13 - 17, 2015; Nashville, Tennessee

TOP STORIES
'Bionic Pancreas' Research Brings Device Closer to Real Life
US Endocrinologists React to Contrave Safety Study Halt

Achieving near normoglycemia in T1DM is ideal for preventing complications, but is challenging. Currently, insulin pump therapy and multiple daily injection therapy are used to control blood glucose levels.
Bionic Pancreas

P: Adults or adolescents with 1 year history of type 1 diabetes and on insulin pump therapy
   Adults at least 21 years of age; adolescents were 12-21 years of age
   No exclusion based on hemoglobin A1c, glycemic stability, major or minor hypoglycemia

I: Patients received therapy with a bionic pancreas for 5 days and therapy with own insulin pump for 5 days
**ARTIFICIAL PANCREAS**
This version of the artificial pancreas, consisting of a continuous glucose monitor, smartphone, and two pumps, was tested in the Beacon Hill study.

**Two Pumps**
Participants wear one pump containing insulin (which lowers blood glucose) and another with glucagon (which raises it). The pumps deliver the medications following commands from the smartphone’s artificial-pancreas app.

**Continuous Glucose Monitor**
This device checks glucose levels just under the skin every few minutes and beams the information to the smartphone.

**Smartphone**
The smartphone contains the artificial-pancreas app. The app uses glucose measurements from the CGM to calculate how much insulin or glucagon to give the user. The smartphone wirelessly sends this information to the two pumps.

Bionic Pancreas

E: Adult study

1° Mean plasma glucose level and mean percentage of time with hypoglycemia while on bionic pancreas

Adolescent study

1° Average of scheduled plasma glucose levels and mean percentage of time glucose levels < 4.0 mmol/L

2° Number of carbohydrate interventions for hypoglycemic episodes
Mean glucose level measured by continuous glucose monitoring
Time in clinically relevant glucose ranges
Fraction of patients with mean glucose level consistent with therapeutic goals of ADA
Bionic Pancreas

• Two co-primary outcomes:
  – Adult study
    • Mean plasma glucose level
      – 7.7 mmol/L (6.4-9.2 mmol/L)
    • Mean percentage of time that the patient had a low glucose level during bionic pancreas period
      – < 4.0 mmol/L 4.8% of the time vs 4.0% in control
      – < 3.3 mmol/L 2.3% of the time vs 1.7% in control
      – 43 carbohydrate interventions (1 every 2.3 days) in BP
      – 68 carbohydrate interventions (1 every 1.5 days) in control
Variation in the Mean Glucose Level among Adults and Adolescents. 

A Mean Glucose Levels in Adults

B Mean Glucose Levels in Adolescents
Table 2. Summary Results of All 5-Day Experiments among Adults and Adolescents.*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Adults (N=20)</th>
<th>Adolescents (N=32)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Bionic Pancreas</td>
<td>Control</td>
</tr>
<tr>
<td></td>
<td>mean</td>
<td>range</td>
</tr>
<tr>
<td><strong>Day and night</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasma glucose on days 1 through 5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean — mg/dl</td>
<td>138±14</td>
<td>116–166</td>
</tr>
<tr>
<td>&lt;60 mg/dl — % of time</td>
<td>2.3±3.2</td>
<td>0–8.9</td>
</tr>
<tr>
<td>&lt;70 mg/dl — % of time</td>
<td>4.8±5.2</td>
<td>0–15.0</td>
</tr>
<tr>
<td>Carbohydrate interventions — no.</td>
<td>2.2±3.2</td>
<td>0–10.0</td>
</tr>
<tr>
<td>Glucose level on continuous monitoring on days 2 through 5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean — mg/dl</td>
<td>133±13</td>
<td>114–152</td>
</tr>
<tr>
<td>&lt;60 mg/dl — % of time</td>
<td>1.5±1.7</td>
<td>0–6.0</td>
</tr>
<tr>
<td>&lt;70 mg/dl — % of time</td>
<td>4.1±3.5</td>
<td>0–12.4</td>
</tr>
<tr>
<td>70–120 mg/dl — % of time</td>
<td>47.7±10.5</td>
<td>29.4–65.5</td>
</tr>
<tr>
<td>70–180 mg/dl — % of time</td>
<td>79.5±8.3</td>
<td>69.3–98.2</td>
</tr>
<tr>
<td>&gt;180 mg/dl — % of time</td>
<td>16.5±7.9</td>
<td>1.8–26.7</td>
</tr>
<tr>
<td>&gt;250 mg/dl — % of time</td>
<td>4.9±3.7</td>
<td>0–12.7</td>
</tr>
<tr>
<td>SD of all individual SDs — mg/dl</td>
<td>53±14</td>
<td>25–73</td>
</tr>
<tr>
<td>Coefficient of variation — %</td>
<td>40±8</td>
<td>22–50</td>
</tr>
<tr>
<td>Mean of daily differences — mg/dl</td>
<td>17±12</td>
<td>4–53</td>
</tr>
</tbody>
</table>

**Nighttime only**

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<td></td>
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<td>range</td>
</tr>
<tr>
<td>Plasma glucose on nights 1 through 5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean — mg/dl</td>
<td>125±19</td>
<td>97–169</td>
</tr>
<tr>
<td>&lt;60 mg/dl — % of time</td>
<td>1.7±5.2</td>
<td>0–22.2</td>
</tr>
<tr>
<td>&lt;70 mg/dl — % of time</td>
<td>4.0±8.0</td>
<td>0–33.3</td>
</tr>
<tr>
<td>Carbohydrate intervention — no.</td>
<td>0.3±0.6</td>
<td>0–2.0</td>
</tr>
<tr>
<td>Level on continuous glucose monitoring on nights 2 through 5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean — mg/dl</td>
<td>126±17</td>
<td>97–170</td>
</tr>
<tr>
<td>&lt;60 mg/dl — % of time</td>
<td>0.4±0.6</td>
<td>0–1.6</td>
</tr>
<tr>
<td>&lt;70 mg/dl — % of time</td>
<td>1.8±2.0</td>
<td>0–8.6</td>
</tr>
<tr>
<td>70–120 mg/dl — % of time</td>
<td>57.1±15.8</td>
<td>28.9–87.0</td>
</tr>
<tr>
<td>70–180 mg/dl — % of time</td>
<td>86.5±10.0</td>
<td>58.1–100</td>
</tr>
<tr>
<td>&gt;180 mg/dl — % of time</td>
<td>11.8±9.5</td>
<td>0–39.8</td>
</tr>
<tr>
<td>&gt;250 mg/dl — % of time</td>
<td>3.6±5.3</td>
<td>0–17.4</td>
</tr>
</tbody>
</table>

* Plus–minus values are means ±SD. To convert the values for glucose to millimoles per liter, multiply by 0.05551.
Bionic Pancreas

• Two co-primary outcomes:
  – Adolescent study
    • Average of scheduled plasma glucose levels
      – Mean level in BP group: 7.7 mmol/L
      – Mean level in control group: 8.7 mmol/L
    • Mean percentage of time that glucose levels were below 4.0 mmol/L
      – BP group: 6.1%
      – Control group: 7.6%
    – 97 carbohydrate interventions (1 every 1.6 days) in BP
    – 210 interventions (1 every 0.8 days) in control
Table 2. Summary Results of All 5-Day Experiments among Adults and Adolescents.*

| Variable | Adults (N=20) | | | Adolescents (N=32) | | |
|----------|---------------|---------------|---------------|---------------|---------------|---------------|---------------|---------------|
|          | Bionic Pancreas | Control | P Value | Bionic Pancreas | Control | P Value | Bionic Pancreas | Control | P Value |
| Day and night | | | | | | | | | | |
| Plasma glucose on days 1 through 5 | | | | | | | | | |
| Mean — mg/dl | 138±14 | 116–166 | | 138±18 | 101–185 | 0.004 | | 157±27 | 103–221 | 0.004 |
| <60 mg/dl — % of time | 2.3±3.2 | 0–8.9 | | 2.6±2.9 | 0–11.5 | 0.40 | | 3.3±5.0 | 0–17.2 | 0.23 |
| <70 mg/dl — % of time | 4.8±5.2 | 0–15.0 | | 6.1±4.5 | 0–20.0 | 0.02 | | 7.6±7.3 | 0–27.6 | 0.001 |
| Carbohydrate interventions — no. | 2.2±3.2 | 0–10.0 | 3.4±3.1 | 0–10.0 | 0.15 | | 3.0±3.3 | 0–15.0 | 6.6±5.8 | 0–20.0 | 0.001 |
| Glucose level on continuous monitoring on days 2 through 5 | | | | | | | | | |
| Mean — mg/dl | 133±13 | 114–152 | 159±30.4 | 105–225 | <0.001 | | 142±12 | 117–179 | 158±27 | 95–222 | 0.004 |
| <60 mg/dl — % of time | 1.5±1.7 | 0–6.0 | 3.7±3.3 | 0–11.5 | 0.02 | | 1.3±1.7 | 0–5.6 | 2.2±3.6 | 0–15.7 | 0.19 |
| <70 mg/dl — % of time | 4.1±3.5 | 0–12.4 | 7.3±4.7 | 0–16.0 | 0.01 | | 3.1±2.7 | 0–9.6 | 4.9±5.1 | 0–24.4 | 0.05 |
| 70–120 mg/dl — % of time | 47.7±10.5 | 29.4–65.5 | 30.8±15.7 | 4.1–67.4 | <0.001 | | 42.0±7.7 | 31.3–63.1 | 30.0±11.8 | 9.6–56.2 | <0.001 |
| 70–180 mg/dl — % of time | 79.5±8.3 | 69.3–98.2 | 58.8±14.6 | 35.1–82.7 | <0.001 | | 75.9±7.9 | 61.4–94.1 | 64.5±14.1 | 29.5–89.5 | <0.001 |
| >180 mg/dl — % of time | 16.5±7.9 | 1.8–26.7 | 33.8±16.4 | 5.7–64.9 | <0.001 | | 21.0±7.0 | 4.9–36.5 | 30.6±15.4 | 1.7–69.3 | 0.002 |
| >250 mg/dl — % of time | 4.9±3.7 | 0–12.7 | 12.3±9.9 | 0.1–32.7 | 0.004 | | 5.9±4.1 | 0–21.4 | 10.8±9.1 | 0–35.6 | 0.001 |
| SD of all individual SDs — mg/dl | 53±14 | 25–73 | 68±18 | 37–102 | 0.01 | | 56±13 | 29–95 | 64±16 | 34–101 | 0.03 |
| Coefficient of variation — % | 40±8 | 22–50 | 43±8 | 34–60 | 0.11 | | 39±7 | 25–53 | 40±8 | 25–58 | 0.54 |
| Mean of daily differences — mg/dl | 17±12 | 4–53 | 43±8 | 34–60 | 0.001 | | 18±18 | 2–81 | 27±13 | 5–61 | 0.03 |
| Nighttime only | | | | | | | | | |
| Plasma glucose on nights 1 through 5 | | | | | | | | | |
| Mean — mg/dl | 125±19 | 97–169 | | 141±20 | 98–190 | 0.02 | | 162±37 | 96–241 | 0.02 |
| <60 mg/dl — % of time | 1.7±5.2 | 0–22.2 | | 1.3±3.4 | 0–10.0 | 0.37 | | 2.2±6.1 | 0–30.0 | 0.37 |
| <70 mg/dl — % of time | 4.0±8.0 | 0–33.3 | | 4.1±6.1 | 0–20.0 | 0.82 | | 4.4±6.7 | 0–30.0 | 0.03 |
| Carbohydrate intervention — no. | 0.3±0.6 | 0–2.0 | 0.6±0.9 | 0–3.0 | 0.17 | | 0.8±1.3 | 0–5.0 | 1.6±1.9 | 0–7.0 | 0.03 |
| Level on continuous glucose monitoring on nights 2 through 5 | | | | | | | | | |
| Mean — mg/dl | 126±17 | 97–170 | 169±52 | 95–286 | 0.002 | | 124±11 | 108–146 | 157±36 | 94–248 | <0.001 |
| <60 mg/dl — % of time | 0.4±0.6 | 0–1.6 | 3.3±4.9 | 0–15.4 | 0.01 | | 1.0±1.4 | 0–4.9 | 1.7±3.5 | 0–17.7 | 0.28 |
| <70 mg/dl — % of time | 1.8±2.0 | 0–8.6 | 6.2±6.7 | 0–21.9 | 0.01 | | 2.6±2.5 | 0–9.4 | 4.0±5.3 | 0–23.7 | 0.16 |
| 70–120 mg/dl — % of time | 57.1±15.8 | 28.9–87.0 | 30.5±20.8 | 0–69.8 | <0.001 | | 55.3±13.7 | 29.9–79.2 | 28.3±17.3 | 0–63.8 | <0.001 |
| 70–180 mg/dl — % of time | 86.5±10.0 | 58.1–100 | 55.6±21.9 | 7.0–83.3 | <0.001 | | 86.9±8.1 | 68.2–99.2 | 66.7±19.9 | 12.8–91.1 | <0.001 |
| >180 mg/dl — % of time | 11.8±9.5 | 0–39.8 | 38.2±25.1 | 1.6–93.0 | <0.001 | | 10.5±7.0 | 0–26.8 | 29.3±22.0 | 0–87.2 | <0.001 |
| >250 mg/dl — % of time | 3.6±5.3 | 0–17.4 | 17.9±20.6 | 0–66.4 | 0.01 | | 1.8±2.5 | 0–9.4 | 9.5±12.5 | 0–42.4 | 0.002 |

* Plus–minus values are means ±SD. To convert the values for glucose to millimoles per liter, multiply by 0.05551.
What this tells us….  

• Better design for bionic pump needed  
• Need to figure out better glucagon
EFFECT OF SITAGLIPTIN ON CARDIOVASCULAR OUTCOMES IN TYPE 2 DIABETES

DOI:10.1056/NEJMoa1501352
Background$^{7,8,9}$

- Previous cardiovascular outcome trials involving DPP-4 inhibitors raised safety concerns of ↑ risk of hospitalization for heart failure
- Meta-analyses reported 24-25% ↑ in risk
TECOS

P: Type 2 diabetes with established cardiovascular disease, at least 50 years of age A1c 6.5-8.0%, treated with 1-2 OHAs or insulin
I: Received sitagliptin 100 mg daily (50 mg if eGFR ≥ 30 - < 50 mL/min) or placebo
Discontinued if ≥ 2 episodes severe hypoglycemia
TECOS

E: 1° First confirmed event of CV death, nonfatal MI, nonfatal stroke, hospitalization for unstable angina

2° First confirmed event of CV death, nonfatal MI or nonfatal stroke

Each individual component of 1° CV outcome, changes in A1c, eGFR, initiation of additional medications, severe hypoglycemia
Results
14,671 included in ITT population
 7,332 receiving sitagliptin
 7,339 receiving placebo
Mean A1c 0.4 % lower in sitagliptin group
Sitagliptin group received less antihyperglycemics and less likely to start long-term insulin
What This Tells Us

• Sitagliptin can be used in patients with Type 2 diabetes at high cardiovascular risk
  – No increase in rates of cardiovascular complications
  – No increase in rates of hospitalization for heart failure
What This Doesn’t Tell Us

• In those that are poorly controlled (A1c > 8.0%), would we see the same results?
• No information on risks/benefits with longer duration of therapy
• No information in patients with more complicated coexisting illness
FDA Drug Safety Communication: FDA warns that SGLT2 inhibitors for diabetes may result in a serious condition of too much acid in the blood

[ 05-15-2015 ]

Safety Announcement

The U.S. Food and Drug Administration (FDA) is warning that the type 2 diabetes medicines canagliflozin, dapagliflozin, and empagliflozin may lead to ketoacidosis, a serious condition where the body produces high levels of blood acids called ketones that may require hospitalization. We are continuing to investigate this safety issue and will determine whether changes are needed in the prescribing information for this class of drugs, called sodium-glucose cotransporter-2 (SGLT2) inhibitors.

Patients should pay close attention for any signs of ketoacidosis and seek medical attention immediately if they experience symptoms such as difficulty breathing, nausea, vomiting, abdominal pain, confusion, and unusual fatigue or sleepiness. Do not stop or change your diabetes medicines without first talking to your prescriber. Health
EUGLYCEMIC DIABETIC KETOACIDOSIS: A POTENTIAL COMPLICATION OF TREATMENT WITH SODIUM-GLUCOSE COTRANSPORTER 2 INHIBITION
Diabetic Ketoacidosis (DKA)
- Hyperglycemia (> 14 mmol/L), anion-gap acidosis, increased plasma ketones

Euglycemic Acidosis
- DKA without hyperglycemia
- Partial treatment of DKA, food restriction, alcohol intake and inhibition of gluconeogenesis
S1&S2 segment
SGLT2
(>90% glucose reabsorbed)

S3 segment
SGLT1
(remaining 10% glucose reabsorbed)

Glomerular capsule
Neck
1st convoluted tubule

Intertubular capillaries
Interlobular vein
Interlobular artery
Spiral tubule

Afferent vessel
Efferent vessel

Irregular tub./ 2nd convol. tub.

Cortical substance

Junctional tub.

Boundary zone

Medullary substance

Ascending limb
Descending limb

Arterial arch
Venous arch
Arteriae rectae

Duct of Bellini

From: Yabe D et al. Short-term impacts of sodium/glucose co-transporter 2 inhibitors in Japanese clinical practice: considerations for their appropriate use to avoid serious adverse events. Expert Opin. Drug Saf. 2015; 14:795-800
## Summary of Case Reports to Date

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>26-64 years</td>
</tr>
<tr>
<td>Gender</td>
<td>8/9 Female</td>
</tr>
<tr>
<td>Diabetes Type</td>
<td>7/9 Type 1</td>
</tr>
<tr>
<td>MDI/CSII</td>
<td>2/9 MDI; 5/9 CSII</td>
</tr>
<tr>
<td>Canagliflozin dose</td>
<td>8/9 300 mg; 1/9 150 mg</td>
</tr>
<tr>
<td>Other contributing factors</td>
<td>Alcohol, Illness, surgery, exercise</td>
</tr>
<tr>
<td>Insulin reduction prior to euDKA</td>
<td>Yes 5/9; No 2/9</td>
</tr>
<tr>
<td>Plasma glucose on admission</td>
<td>5.3 – 12.9 mmol/L</td>
</tr>
<tr>
<td>Ketones</td>
<td>Yes 9/9</td>
</tr>
</tbody>
</table>

What to do?

• SGLT-2 inhibitors not indicated for use in Type 1 diabetes

• If determined benefits > risks:
  – Need to check for ketones
    • Feeling unwell
    • More than minimal alcohol consumption
    • Reduction of insulin doses
  – Ketones present
    • Withhold SGLT-2 inhibitor
    • Hydrate
    • Consume carbohydrates to allow full dose insulin
What to do?

• In Type 2 diabetes
  – No need to check for ketones daily
  – May need to discontinue in pre-operatively
    • Unsure of timeframe

Evaluate all patients displaying nausea, vomiting, shortness of breath or malaise for ketones
References


