How Diabetes Drugs are Changing the Landscape: A Nephrologist’s Perspective

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Conflict of Interest Disclosure
I have no conflicts and nothing to disclose

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Case
Case
• HTN
• Type II DM
• Afib/flutter
• EF of 10-15%

Insulin
Warfarin
Spironolactone
Metoprolol
Furosemide (doubled PTA)
Metolazone (added PTA)
Metformin

Physical Exam

BNP was 872 pg/mL (1-138 pg/mL)

Noted conversational dyspnea
3 wks earlier:
Creatinine was 1.23 mg/dl

Diagnosis:
Decompensated CHF
Hours into admission…

- Increasing SOB and agitation
- Progressive hypotension
- Vasopressors

\[
\begin{array}{c|c|c|c}
\text{Hct} & \text{Hgb} & \text{Hmo} \\
137 & 89 & 34 \\
6.2 & 4 & 1.62 \\
\end{array}
\]

ABG: 6.97/26
Lactate: 12.7 mmol/L

Initial Labs revisited…

\[
\begin{array}{c|c|c|c|c}
\text{Hct} & \text{Hgb} & \text{Hmo} \\
136 & 95 & 24 \\
4.3 & 20 & 1.5 \\
\end{array}
\]

AG = 21
Anion Gap Metabolic Acidosis (AGMA)

M - methanol
U - uremia
D - DKA/AKA
P - paraldehyde
I - iron/INH
L - lactic acidosis
E - ethylene glycol
S - salicylates

G - glycols
O - oxoprolene
L - L-lactate
D - D-lactate
M - methanol
A - aspirin
R - renal failure
K - ketoacidosis

Pyruvate
Lactate $20 \text{ mmol/kg/day}$

$70\%$

$30\%$

**CORI CYCLE**

Glucos $ \rightarrow $ Lactate $ \rightarrow $ Glucos $30\%$ $70\%$

**Maximum Lactate Utilization** $\approx 300 \text{ mmol/h}$

**Causes of Lactic Acidosis**
Lactic Acidosis

Type A
O₂ supply/demand

Type B
Rx
Biguanides

- *Galega officinalis*
  - Guanidine
  - Phenformin
  - Metformin
  - Goat’s rue
  - French lilac
  - Professor weed

- Metformin-associated LA (MALA)
- Metformin-induced LA (MILA)
Risk Factors for MILA

- Low GFR
- Advanced Age
- Liver Disease and/or ETOH use
- Heart Failure
- Decreased Tissue Perfusion
- Hypoxemia or critical illness

Clinical Outcomes of Metformin Use in Populations With Chronic Kidney Disease, Congestive Heart Failure, or Chronic Liver Disease: A Systematic Review

Conclusion: Metformin use in patients with moderate CKD, CHF, or CLD with hepatic impairment is associated with improvements in key clinical outcomes. Our findings support the recent changes in metformin labeling.
CASE 2

40 y/o male
- Fever
- Malaise
- Confusion
- LE Draining Wound

40 y/o with fever, malaise, confusion, LE wound

Glucose
Ketones
D₅W with 150 mEq/L sodium bicarbonate and Abx

Hospital Course

ABG: 7.24 / 16

DON'T TRY TO PULL OUT EVERY THREE MINUTES
FDA warns that SGLT2 inhibitors for diabetes may result in a serious condition of too much acid in the blood

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 care professionals should evaluate for the presence of acidosis, including ketoacidosis, in patients experiencing these signs or symptoms; discontinue SGLT2 inhibitors if acidosis is confirmed; and take appropriate measures to correct the acidosis and monitor sugar levels.

SGLT2 inhibitors are a class of prescription medicines that are FDA-approved for use with diet and exercise to lower blood sugar in adults with type 2 diabetes. When untreated, type 2 diabetes can lead to serious problems, including blindness, nerve and kidney damage, and heart disease. SGLT2 inhibitors lower blood sugar by causing the kidneys to remove sugar from the body through the urine. These medicines are available as single-ingredient products and also in combination with other diabetes medicines such as metformin (see Table 1 below). The safety and efficacy of SGLT2 inhibitors have not been established in patients with type 1 diabetes, and FDA has not approved them for use in these patients.

A search of the FDA Adverse Event Reporting System (FAERS) database identified 20 cases of acidosis reported as diabetic ketoacidosis (DKA), ketoacidosis, or ketosis in patients treated with SGLT2 inhibitors from March 2013 to June 6, 2014 (see Data Summary). All patients required emergency room visits or hospitalization to treat the ketoacidosis. Since June 2014, we have continued to receive additional FAERS reports for DKA and ketoacidosis in patients treated with SGLT2 inhibitors.
But wait…

- Proximal Tubule is the sole site of glucose reabsorption
  - SGLT1 found in S3 of proximal tubule
    Reabsorbs 10-20% of filtered glucose
  - SGLT2 found in S1 and S2 of proximal tubule
    Reabsorbs 80-90% of filtered glucose

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Increased glucose reabsorption increases salt retention.

Glucose reabsorption is driven by sodium reabsorption.

Chloride moves passively in response to sodium resorption.

Increased glucose reabsorption increases salt retention.

SGLT2 Inhibitors

Empagliflozin and Canagliflozin are SGLT2 inhibitors.

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SGLT2 inhibitors decrease glucose reabsorption and are also diuretics.

Increased GFR results in hyperglycemia.

Hyperfiltration

Increased glucose, sodium, and chloride reabsorption at the proximal tubule.

Increased intraglomerular pressure.

Macula densa detects decreased delivery of chloride.

Dilate.
correction of hyperfiltration

ACEi / ARB
- dilation of the afferent arteriole
- constriction of the efferent arteriole
- decreased intraglomerular pressure
- immediate decrease in GFR
- better renal outcomes

SGLT2i
- decreased intraglomerular pressure
- immediate decrease in GFR
- better renal outcomes
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### Primary Outcome: Benefits in eGFR 30 to <45 Subgroup

<table>
<thead>
<tr>
<th>Screening eGFR</th>
<th>Hazard ratio (95% CI)</th>
<th>Interaction P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 to &lt;45 mL/min/1.73 m²</td>
<td>0.75 (0.59–0.95)</td>
<td>0.11</td>
</tr>
<tr>
<td>45 to &lt;60 mL/min/1.73 m²</td>
<td>0.52 (0.38–0.72)</td>
<td>0.52</td>
</tr>
<tr>
<td>60 to &lt;90 mL/min/1.73 m²</td>
<td>0.82 (0.60–1.12)</td>
<td>0.62</td>
</tr>
</tbody>
</table>

**NNT in patients with eGFR 30 to <45 mL/min/1.73 m²**

Favors Canagliflozin  Favors Placebo

NNT: 16
American College of Cardiology recommends empagliflozin as preferred SGLT2 inhibitor for adults with type 2 diabetes and established cardiovascular disease in new Expert Consensus Decision Pathway.