SGLT2 Inhibitors: Mechanism of Action, Pros, and Cons

April 03, 2014
By Veronica Hackethal, MD [1]

Sodium glucose cotransporter 2 inhibitors act independently of insulin level and so can be used at various stages of type 2 diabetes disease progression. Latest findings, here.

Sodium glucose cotransporter 2 (SGLT2) inhibitors are among the newest classes of oral agents to treat type 2 diabetes mellitus (T2DM). In early 2013, the FDA approved canagliflozin (Invokana), followed in January 2014 by approval of dapagliflozin (Forxiga). A third SGLT2 inhibitor, empagliflozin, is currently under review.

SGLT inhibitors block the SGLT2 protein involved in 90% of glucose reabsorption in the proximal renal tubule, resulting in increased renal glucose excretion and lower blood glucose levels. These agents probably also increase insulin sensitivity, decrease gluconeogenesis, and improve insulin release from pancreatic beta cells.

The results of several recent studies seem to parallel those of pre-marketing studies. Advantages of SGLT2 inhibitors include:

- Insulin-independent action: allows SGLT2 inhibitors to be used at various stages during the progression of T2DM
- Improved glycemia, A1C reductions: ranging from 0.6% to nearly 1% in some studies
- Mild reduction in blood pressure, possibly related to sodium loss
- Low risk of hypoglycemia
- Modest weight loss

Recent studies have also confirmed the main adverse effects of SGLT2 inhibitors:

- Mycotic genital infections and urinary tract infections secondary to glucosuria
- Polyuria: possible increased risk of renal impairment secondary to dehydration
- Volume depletion: hypotension, dizziness, fainting
- Cardiovascular: possible increased risk of ischemic stroke within the first 30 days of treatment, according to interim results from the Canagliflozin Cardiovascular Assessment Study (CANVAS)
- Contraindicated in T1DM, patients prone to urinary ketones or hematuria, or those with severe renal impairment

**Surprising Findings**

Unexpected results related to the homeostatic effects of SGLT2 inhibitors have been reported in 2 recent studies. Both report that SGLT2 inhibitors seem to paradoxically increase glucagon levels and production of endogenous glucose.

In the first study, Ferrannini and colleagues in Italy and Germany evaluated 66 patients with T2DM who received a 5-hour meal tolerance test followed by a 3-hour fasting period. Participants were evaluated after receiving a single dose and following 4-week treatment with empagliflozin. Key results included:

- Increased insulin sensitivity
- Significantly increased glucagon response
- An increase in endogenous glucose production of approximately 25% after 3 hours of fasting
- After 4 weeks of treatment, HbA1C and fasting glucose levels declined significantly, the increase in endogenous glucose production slowed, and the rise in glucagon, although still increased, was also blunted

The authors emphasized that the rise in endogenous glucose production balanced the amount of glucose lost through renal excretion. Without the rise in endogenous glucose production, they estimated, postprandial glucose levels would have decreased by about 50% instead of 12%, as observed in the study.

In a similar study, Merovci and colleagues at the University of Texas Health Science Center assessed 18 diabetic men randomized to either dapagliflozin or placebo for 2 weeks. Key results indicated that dapagliflozin:

- Markedly lowered fasting plasma glucose level, improved muscle insulin sensitivity, and increased insulin-mediated tissue glucose disposal by about 18%
Increased endogenous glucose production: by day 3 the amount produced was approximately half the glucose excreted renally secondary to SGLPT2 inhibition.

Increased glucagon level by 23%
The authors estimated that had the increase in endogenous glucose production not occurred, dapagliflozin would have had double the effect on lowering fasting plasma glucose levels.

“A decrease in fasting plasma glucose concentration potentially could lead to an increase in hepatic glucose production, due to removal of the inhibitory effect of hyperglycemia on hepatic glucose production,” the authors wrote. “This raises the interesting possibility of the existence of a novel reflex arc—either directly or neurally mediated between the kidney and the liver/pancreas.”

One possible strategy to counteract this effect, the authors suggested, would be to combine SGLT2 inhibitors with the glucagon-inhibiting properties of incretin mimetics.

**SGLT2 Inhibitors as Add-on Therapy**

Studies looking at add-on treatment with SGLT2 inhibitors have found their effects on glycemic control to be roughly additive. Recent examples include:

**Canagliflozin with metformin and pioglitazone:** A randomized, double-blind, phase 3 study of 342 patients already receiving metformin and pioglitazone who received canagliflozin or placebo over a 26-week period. Results showed that canagliflozin at doses of 100 or 300 mg significantly lowered HbA1c by about −0.89%.

**Canagliflozin with metformin, compared with glimepiride:** In a 52 week, randomized, double-blind, phase 3 trial of patients inadequately controlled on metformin in 19 countries, canagliflozin 100 mg was similar to glimepiride in lowering HbA1c, and canagliflozin 300 mg provided greater HbA1c reductions than glimepiride.

**Dapagliflozin with metformin:** A systematic literature review of RCTs with diabetes patients inadequately controlled with metformin found that dapagliflozin had a similar effect on HbA1c after 1 year, compared with DPP-4 inhibitors, thiazolidinediones, sulphonylureas, and GLP-1 inhibitors.

**Dapagliflozin with insulin:** A 24-week, randomized, placebo-controlled, double-blind trial with 808 patients found that mean HbA1c decreased by −0.6% to −0.8% with dapagliflozin therapy after 104 weeks. Insulin dose increased in the placebo group, but remained stable in the dapagliflozin group.

**Take-Home Points**

SGLT2 inhibitors:

- Induce glycosuria, improve glycemia, reduce A1C levels, have low risk of hypoglycemia, and modestly reduce weight and blood pressure.
- Increase the risk of genital mycotic infections, polyuria, and volume depletion, and may increase the risk of ischemic stroke, especially early in treatment.
- Could increase glucagon levels and endogenous glucose production, although the mechanism remains unclear.
- As add-on therapy, could improve glycemic control and help stabilize insulin dosage.

**References:**


Links:
[1] [http://www.diagnosticimaging.com/authors/veronica-hackethal-md-0](http://www.diagnosticimaging.com/authors/veronica-hackethal-md-0)