

SODIUM GLUCOSE CO-TRANSPORTER 2 (SGLT2) INHIBITORS

A Novel Class of Antidiabetic Agents

Lisa Brown, Pharm.D.
 PGY-1 Pharmacy Practice Resident
 Palm Beach Atlantic University
 Lloyd L. Gregory School of Pharmacy

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

Pharmacologic Agent	Year of FDA-Approval
Humulin R, HumulinN	1982
Glipizide	1984
Metformin	1994
Acarbose	1995
Actos® (pioglitazone)	1999
Byetta® (exenatide)	2005
Januvia™ (sitagliptin)	2006

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

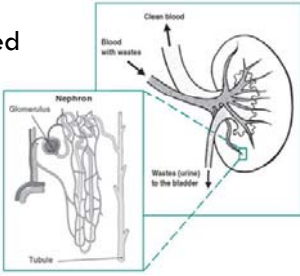
GENE	PROTEIN	SUBSTRATES	TISSUE DISTRIBUTION
SLC5A1	SGLT1	Glucose, galactose	SI, heart, trachea, kidney
SLC5A2	SGLT2	Glucose	Kidney
SLC5A4	SGLT3	Glucose sensor	SI, uterus, lungs, thyroid, testis
SLC5A9	SGLT4	Mannose, glucose, fructose, 1,5-AG, galactose	SI, kidney, liver, stomach, lung
SLC5A10	SGLT5	Glucose, galactose	Kidney
SLC5A11	SGLT6	Myo-inositol, glucose, xylose, chiro-inositol	Spinal cord, kidney, brain, SI

1,5-AG:1,5-anhydro-d-glucitol; SLC5A: solute carrier family 5A; SI: small intestine

Adapted from Jabbour SA, et al. Int J ClinPract 2008;1279-1284.

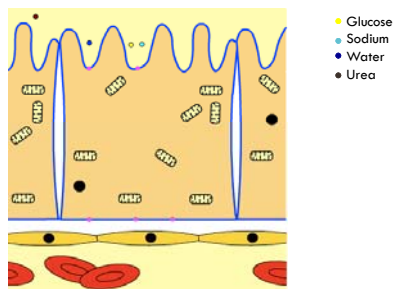
Sodium Glucose Co-Transporter 2 (SGLT2)

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



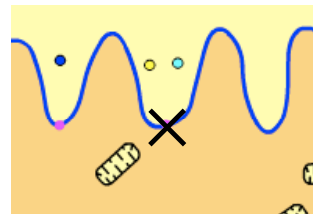
<http://kidney.niddk.nih.gov>

Sodium Glucose Co-Transporter 2 (SGLT2) Con't...



<http://www.biologymad.com/resources/kidney.swf>

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

Potential Clinical Advantages

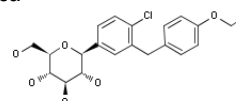
4. Weight loss
 - Advantage over insulin, sulfonylureas, and TZDs
5. No gastrointestinal adverse effects
 - Advantage over metformin
6. Osmotic diuretic effect
 - Advantage in patients with CHF

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

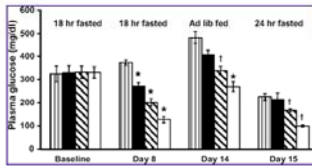


FIG. 5. Dapagliflozin lowers fasting and fed plasma glucose over 15 days of once-daily oral treatment in ZDF rats. □, Vehicle; ■, 0.01 mg/kg; ▨, 0.1 mg/kg; □, 1 mg/kg. *P < 0.0001, †P < 0.05, each vs. vehicle.

Adapted from Songping H, et al. Diabetes 2008;57:1723-1729

Dapagliflozin: Phase IIa Study

- Four treatment groups:

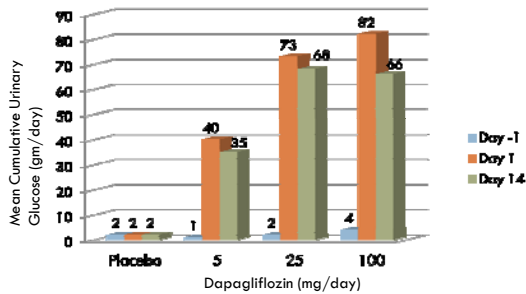
- Placebo (n=8)
- Dapagliflozin 5mg/day (n=11)
- Dapagliflozin 25mg/day (n=12)
- Dapagliflozin 100mg/day (n=16)

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

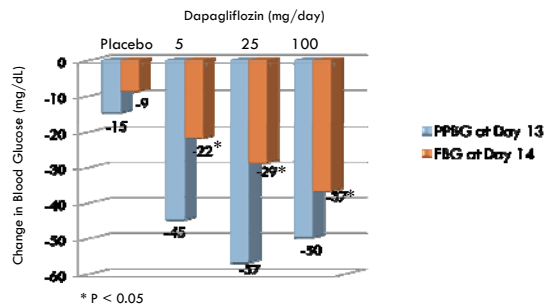
Adapted from Jebbour SA, et al. Int J ClinPract 2008;1279-1284.

Phase IIa Study Con't... 24-Hour Urinary Glucose Excretion



Adapted from Fonseca VA, American Association of Clinical Endocrinology

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



* 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
 - Vulvovaginal 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 (±47)
 - Dapagliflozin 100mg group: increased by + 10 mEq (±67)
 - No change in other urine or plasma electrolytes

Ongoing Clinical Trials

Phase	Study Description	Study Design	Start Date	Completion Date
III	Efficacy and safety of dapagliflozin in patients uncontrolled on metformin alone	Randomized, double-blind, placebo-controlled, parallel group	September 2007	November 2008
III	Dapagliflozin in patients uncontrolled with diet and exercise alone	Randomized, double-blind, parallel group	September 2007	February 2009
III	Efficacy and safety of dapagliflozin in combination with metformin XR	Randomized, double-blind, active control, parallel group	March 2008	August 2009
III	Efficacy and safety of dapagliflozin in combination with metformin	Randomized, double-blind, parallel group	March 2008	February 2011
III	Efficacy and safety of dapagliflozin in patients uncontrolled on insulin alone	Randomized, double-blind, parallel group	April 2008	March 2010

www.clinicaltrials.gov

Ongoing Clinical Trials Con't...

Phase	Study Description	Study Design	Start Date	Completion Date
III	Efficacy and safety of dapagliflozin in combination with glimeperide	Randomized, double-blind, parallel group	April 2008	May 2010
III	Efficacy and safety of dapagliflozin as monotherapy	Randomized, double-blind, placebo-controlled, parallel group	September 2008	January 2010
I	Pharmacokinetics and pharmacodynamics of dapagliflozin in patients with renal impairment	Randomized, double-blind, placebo-controlled, parallel group	September 2007	February 2009
II	Glycemic efficacy and renal safety of dapagliflozin in patients with moderate renal impairment	Randomized, double-blind, parallel group	April 2008	December 2009

www.clinicaltrials.gov

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

Potential Place in Therapy

- May be useful in patients with type 2 or 1 diabetes
 - FDA-approval being sought for patients with type 2 diabetes
- Monotherapy or in combination with other agents
 - Degree of effect on Hemoglobin A1C uncertain

References

1. Fonseca VA. Efficacy and safety of SGLT2 inhibition: evidence from trials and nature. Online CE Presentation, American Association of Clinical Endocrinologists 2008. Accessed at www.medscape.com.
2. Fujimori Y, Katsumo K, Nakashima I, et al. Remogliflozinetabonate, in a novel category of selective low-affinity sodium glucose cotransporter (SGLT2) inhibitors, exhibits antidiabetic efficacy in rodent models. *J Pharmacol Exp Ther* 2008;327(1):268-276.
3. Hussey EK, Clark RV, Amin DM, et al. Early clinical studies to assess the safety, tolerability, pharmacokinetics and pharmacodynamics of single doses of sergliflozin, a novel inhibitor of renal glucose reabsorption, in healthy volunteers and subjects with type 2 diabetes mellitus. Chicago, IL: American Diabetes Association, 67th Annual Scientific Sessions, 2007, 0189-096.
4. Jabbour SA, Goldstein BJ. Sodium glucose co-transporter 2 inhibitors: blocking renal tubular reabsorption of glucose to improve glycemic control in patients with diabetes. *Int J Clin Pract* 2008;62(8):1279-1284.
5. Katsumo K, Fujimori Y, Takemura Y, et al. Sergliflozin, a novel selective inhibitor of low-affinity sodium glucose cotransporter (SGLT2), validates the critical role of SGLT2 in renal glucose reabsorption and modulates plasma glucose level. *J Pharmacol Exp Ther* 2007;320(1):323-330.
6. Komarowski B, Brenner E, Li L, et al. Dapagliflozin (BMS-512148), a selective inhibitor of the sodium-glucose uptake transporter 2 (SGLT2), reduces fasting serum glucose and glucose excursion in type 2 diabetes mellitus patients over 14 days. Chicago, IL: American Diabetes Association, 67th Annual Scientific Sessions, 2007, 0188-OR.
7. Pajor AM, Randolph KM, Kerner SA et al. Inhibitor binding in the human renal low- and high affinity Na⁺/glucose cotransporters. *J Pharmacol Exp Ther* 2008;324(3):985-991.
8. Songping H, Hagan DL, Taylor JR, et al. Dapagliflozin, a selective SGLT2 inhibitor, improves glucose homeostasis in normal and diabetic rats. *Diabetes* 2008;57:1723-1729.

True/False Questions

1. 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.
2. Potential candidates for SGLT2 inhibitors include patients with diabetes who are obese, edematous, or suffer from hypoglycemic episodes or gastrointestinal adverse effects from other antidiabetic agents.
3. Data from pharmacokinetic studies has confirmed that Dapagliflozin is safe in patients with renal impairment.