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New Class of Drug for Type 2 Diabetes Acts Independent of Insulin

Fran Lowry

June 28, 2010 (Orlando, Florida) — Dapagliflozin, a new type of drug for the treatment of type 2 diabetes, improves glycemic control independent of insulin by reducing renal glucose reabsorption, according to a new phase 3 study presented here at the American Diabetes Association 70th Scientific Sessions and published concurrently in the June 26 issue of *The Lancet*.

Given with metformin, dapagliflozin represents a new therapeutic option for the treatment of patients with type 2 diabetes who have inadequate glycemic control with metformin alone, said Clifford J. Bailey, PhD, from Aston University, Birmingham, United Kingdom.

Dapagliflozin, which is a selective sodium-glucose cotransporter-2 inhibitor, works by preventing reabsorption of glucose in the kidneys and promotes the excretion of glucose in the urine. It thereby reduces high levels of blood glucose without affecting insulin-dependent systems.

"Many complications of diabetes are related to high concentrations of blood glucose, so being able to lower blood glucose is a legitimate target for new drugs for diabetes. This is a new class of agent to treat diabetes. It works in a non-insulin-dependent manner, [lowering] glucose levels by increasing the elimination of excess glucose in the urine," Dr. Bailey told *Medscape Diabetes & Endocrinology*. "Because it is a non-insulin-dependent mechanism, it should be suitable for use at any time during the duration of the disease process, and it should be compatible with an additive to any of the other therapies that we have available at the moment."

The multicenter study included 534 adults with type 2 diabetes who were receiving at least 1500 mg of metformin per day but still had poor glycemic control. The participants were randomly assigned to receive 1 of 3 doses of dapagliflozin (2.5 mg, n = 135; 5 mg, n = 133, or 10 mg, n = 132) or placebo (n = 134) orally once daily, in addition to receiving their prestudy metformin dosing.

The primary outcome measure was change from baseline in hemoglobin A1c (HbA1c) at 24 weeks.

The study found that mean HbA1c had decreased by -0.30% (95% confidence interval [CI], -0.44 to -0.16) in the placebo group compared with -0.67% (95% CI, -0.81 to -0.53; *P* =

.0002) in the dapagliflozin 2.5 mg group, -7.0% (95% CI, -0.85 to 0.56; $P < .0001$) in the dapagliflozin 5 mg group, and -0.84% (95% CI, -0.98 to -0.70; $P < .0001$) in the dapagliflozin 10 mg group.

Hypoglycemia was reported at similar frequency in both groups. However, symptoms of genital infections were more common in the dapagliflozin groups, occurring in 8% to 13% of individuals compared with in 5% of the participants in the placebo group.

"This is likely to reflect the extra glucose that is eliminated in the urine," Dr. Bailey commented.

Asked whether these infections might pose a problem, Dr. Bailey commented that patients did not describe these infections as problematic. "As far as I am aware, although I don't have the data in my hand at the moment, there was some evidence of some osmotic diuresis at the beginning of therapy, but patients did not report any particular problem associated with this," he said.

There were no changes in the measures of renal function in any of the groups, and serious adverse events occurred in 17 patients (4 in each of the dapagliflozin groups and 5 in the placebo group).

The study also found that individuals receiving dapagliflozin lost more weight than those randomly assigned to placebo. Mean weight loss was 0.9 kg per person in the placebo group compared with 2.2 kg in the dapagliflozin 2.5 mg group, 3.0 kg in the 5 mg group, and 2.9 kg in the 10 mg group.

Commenting on this study for *Medscape Diabetes & Endocrinology*, Sue Kirkman, MD, from the American Diabetes Association, Alexandria, Virginia, called it an "intriguing" study.

"It is interesting to have a drug that does not work through insulin or on insulin," Dr. Kirkman said in an interview, stressing that her opinions were hers, and not those of the American Diabetes Association. "I actually was wondering as he was talking whether dapagliflozin would have any role in treating type 1 diabetes as well."

She added that the drug appears to have a good safety profile, but that time will be the proof. "In all the studies that I've seen so far — including the animal studies — it looks very safe. But I think we all have concerns about long-term use. We need to make sure that it doesn't have any bad effects on the kidney or that urinary tract infections aren't an ongoing problem, because there definitely is a trend. People with diabetes are prone to infections and kidney problems anyway, and we certainly want to make sure that those aren't long-term problems. But it's certainly an interesting class of drugs and may become part of the armamentarium."

The study was supported by Bristol-Myers Squibb and AstraZeneca. Dr. Bailey disclosed financial relationships with Bristol-Myers Squibb; AstraZeneca; Merck, Sharp & Dohme; Novo Nordisk; GlaxoSmithKline; Takeda; sanofi-aventis; and Merck Serono. Dr. Kirkman has disclosed no relevant financial relationships.

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