

Tenofovir Gel Effective During Term Pregnancy

BY DOUG BRUNK

FROM THE ANNUAL MEETING OF THE
INFECTIOUS DISEASES SOCIETY FOR
OBSTETRICS AND GYNECOLOGY

SANTA FE, N.M. — A single application of tenofovir 1% vaginal gel in term pregnancy produces low serum levels consistent with those reported in nonpregnant women, results from a small single-center trial demonstrated.

The findings come just weeks after a study published online in the journal *Science* found that 1% tenofovir gel used before and after sexual intercourse reduced HIV in women by 39% and reduced the incidence of herpes simplex virus type 2 infections by 50% (*Science* 2010 July 20 [doi:10.1126/science.1193748]). “It does appear that tenofovir gel, once absorbed, does get to the fetal compartment, with very low overall cord blood levels—ap-

proximately 40-fold lower than you see after oral dosing—with a very similar cord:maternal blood ratio,” Dr. Richard Beigi said at the meeting.

“In addition, it appears that single-dose tenofovir appears very safe in term pregnancy. These findings justify continued investigation of this product in pregnancy,” he said.

In a phase I trial conducted by the Microbicide Trials Network, researchers

evaluated 16 healthy pregnant women who were scheduled to undergo cesarean delivery at term gestation between August 2008 and January 2010.

The women received a single 4-g application of tenofovir 1% vaginal gel preoperatively.

“Oral tenofovir has a growing record of safety,” he said. “It’s a category B drug, with close to 1,000 exposures collected in the Antiretroviral Pregnancy Registry. So we felt very comfortable moving [the gel form of] this drug into pregnancy trials.”

Dr. Beigi of the department of obstetrics, gynecology and reproductive sciences at the University of Pittsburgh and his associates collected maternal blood for serum drug concentrations at baseline and at 1, 2, 4, 6, 8, 12, and 24 hours. They also collected specimens of



‘Single-dose tenofovir appears very safe in term pregnancy. These findings justify continued investigation.’

DR. BEIGI

amniotic fluid, cord blood, placenta, and endometrium during surgery, and collected data on maternal and neonatal adverse events.

All 16 women had detectable levels in the serum after vaginal placement. The median maternal concentration of tenofovir was 4.3 ng/mL, “which is very low,” Dr. Beigi said. “The median time to get that concentration was approximately 4 hours. To put this in perspective, when a mom takes a single oral dose of 600-mg tenofovir, their median concentration is 440 ng/mL. So we’re looking at levels that are approximately 100-fold lower.”

The median cord:maternal blood ratio was 0.53, which is approximately the same as with oral dosing of tenofovir. ■

VITALS

Major Finding: The median maternal serum concentration of 1% tenofovir vaginal gel was 4.3 ng/mL, which is about 100-times lower than a single 600-mg dose of oral tenofovir.

Data Source: A phase I trial of 16 healthy pregnant women who were scheduled to undergo cesarean delivery at term gestation and who received a single 4-g application of tenofovir 1% vaginal gel preoperatively.

Disclosures: The study was funded by the National Institute of Allergy and Infectious Diseases, the Eunice Kennedy Shriver National Institute of Child Health and Human Development, and the National Institute of Mental Health. The nonprofit organization CONRAD supplied the tenofovir gel. Dr. Beigi said that he had no relevant financial disclosures to make.

LANTUS®

(insulin glargine [rDNA origin] injection) solution for subcutaneous injection

The following are examples of drugs that may increase the blood-glucose-lowering effect of insulins including LANTUS and, therefore, increase the susceptibility to hypoglycemia: oral anti-diabetic products, pramlintide, angiotensin converting enzyme (ACE) inhibitors, disopyramide, fibrates, fluoxetine, monoamine oxidase inhibitors, propoxyphene, pentoxifylline, salicylates, somatostatin analogs, and sulfonamide antibiotics.

The following are examples of drugs that may reduce the blood-glucose-lowering effect of insulins including LANTUS: corticosteroids, niacin, danazol, diuretics, sympathomimetic agents (e.g., epinephrine, albuterol, terbutaline), glucagon, isoniazid, phenothiazine derivatives, somatropin, thyroid hormones, estrogens, progestogens (e.g., in oral contraceptives), protease inhibitors and atypical antipsychotic medications (e.g. olanzapine and clozapine).

Beta-blockers, clonidine, lithium salts, and alcohol may either potentiate or weaken the blood-glucose-lowering effect of insulin. Pentamidine may cause hypoglycemia, which may sometimes be followed by hyperglycemia.

The signs of hypoglycemia may be reduced or absent in patients taking sympatholytic drugs such as beta-blockers, clonidine, guanethidine, and reserpine.

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C: Subcutaneous reproduction and teratology studies have been performed with insulin glargine and regular human insulin in rats and Himalayan rabbits. Insulin glargine was given to female rats before mating, during mating, and throughout pregnancy at doses up to 0.36 mg/kg/day, which is approximately 7 times the recommended human subcutaneous starting dose of 10 Units/day (0.008 mg/kg/day), based on mg/m². In rabbits, doses of 0.072 mg/kg/day, which is approximately 2 times the recommended human subcutaneous starting dose of 10 Units/day (0.008 mg/kg/day), based on mg/m², were administered during organogenesis. The effects of insulin glargine did not generally differ from those observed with regular human insulin in rats or rabbits. However, in rabbits, five fetuses from two litters of the high-dose group exhibited dilation of the cerebral ventricles. Fertility and early embryonic development appeared normal.

There are no well-controlled clinical studies of the use of LANTUS in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. It is essential for patients with diabetes or a history of gestational diabetes to maintain good metabolic control before conception and throughout pregnancy. Insulin requirements may decrease during the first trimester, generally increase during the second and third trimesters, and rapidly decline after delivery. Careful monitoring of glucose control is essential in these patients.

8.3 Nursing Mothers

It is unknown whether insulin glargine is excreted in human milk. Because many drugs, including human insulin, are excreted in human milk, caution should be exercised when LANTUS is administered to a nursing woman. Use of LANTUS is compatible with breastfeeding, but women with diabetes who are lactating may require adjustments of their insulin doses.

8.4 Pediatric Use

The safety and effectiveness of subcutaneous injections of LANTUS have been established in pediatric patients (age 6 to 15 years) with type 1 diabetes [see *Clinical Studies (14) in the full prescribing information*]. LANTUS has not been studied in pediatric patients younger than 6 years of age with type 1 diabetes. LANTUS has not been studied in pediatric patients with type 2 diabetes.

Based on the results of a study in pediatric patients, the dose recommendation when switching to LANTUS is the same as that described for adults [see *Dosage and Administration (2.3) and Clinical Studies (14) in the full prescribing information*]. As in adults, the dosage of LANTUS must be individualized in pediatric patients based on metabolic needs and frequent monitoring of blood glucose.

8.5 Geriatric Use

In controlled clinical studies comparing LANTUS to NPH insulin, 593 of 3890 patients (15%) with type 1 and type 2 diabetes were ≥65 years of age and 80 (2%) patients were ≥75 years of age. The only difference in safety or effectiveness in the subpopulation of patients ≥65 years of age compared to the entire study population was a higher incidence of cardiovascular events typically seen in an older population in both LANTUS and NPH insulin-treated patients.

Nevertheless, caution should be exercised when LANTUS is administered to geriatric patients. In elderly patients with diabetes, the initial dosing, dose increments, and maintenance dosage should be conservative to avoid hypoglycemic reactions. Hypoglycemia may be difficult to recognize in the elderly [See *Warnings and Precautions (5.3)*].

10. OVERDOSAGE

An excess of insulin relative to food intake, energy expenditure, or both may lead to severe and sometimes prolonged and life-threatening hypoglycemia. Mild episodes of hypoglycemia can usually be treated with oral carbohydrates. Adjustments in drug dosage, meal patterns, or exercise may be needed.

More severe episodes of hypoglycemia with coma, seizure, or neurologic impairment may be treated with intramuscular/subcutaneous glucagon or concentrated intravenous glucose. After apparent clinical recovery from hypoglycemia, continued observation and additional carbohydrate intake may be necessary to avoid recurrence of hypoglycemia.

Rev. September 2009
sanofi-aventis U.S. LLC
Bridgewater, NJ 08807
©2009 sanofi-aventis U.S. LLC

GLA-BPLR-AS2-SEP09