

Excess Risk of GBS Low With H1N1 Vaccine

BY MICHELE G. SULLIVAN

FROM THE MMWR

The excess risk of developing Guillain-Barré syndrome associated with receipt of the pandemic influenza A(H1N1) vaccine is less than 1 case per 1 million vaccinations—a rate comparable to that seen for some trivalent seasonal influenza vaccines.

Preliminary results released in the Mor-

bidity and Mortality Weekly Report found 326 confirmed new cases of the neurological disorder from Oct. 1, 2009 through May 10, 2010 (MMWR 2010;59:1-5).

Of these patients, 27 reported having had the pandemic flu vaccine within 42 days of the onset of GBS—the time period considered plausible for any biologic link between the two. Most of these patients reported an antecedent illness typically related to GBS onset

(gastrointestinal illness or respiratory infection).

“Notably, this high proportion of antecedent illnesses associated with GBS suggests that a number of the GBS illnesses observed after vaccination might be attributable to other antecedent illnesses,” wrote C. Prothro of the California Emerging Infections Program, Oakland, and co-authors. “Historically, 40%-70% of GBS patients report experi-

encing antecedent infectious illness.”

If the preliminary analysis is confirmed—which the CDC expects to happen by this fall—then the attributable rate of GBS would be 0.71 per 100,000 person-years, corresponding to an excess GBS rate of 0.8 cases per 1 million vaccinations, the report said.

Although the report deemed the risk of vaccination-related GBS to be low with pandemic flu vaccine, it did recommend caution for patients with GBS who might consider vaccination.

“Persons with a history of GBS should discuss potential risks and benefits with

• *Insulin initiation and intensification of glucose control*

Intensification or rapid improvement in glucose control has been associated with a transitory, reversible ophthalmologic refraction disorder, worsening of diabetic retinopathy, and acute painful peripheral neuropathy. However, long-term glycemic control decreases the risk of diabetic retinopathy and neuropathy.

• *Lipodystrophy*

Long-term use of insulin, including LANTUS, can cause lipodystrophy at the site of repeated insulin injections. Lipodystrophy includes lipohypertrophy (thickening of adipose tissue) and lipoatrophy (thinning of adipose tissue), and may affect insulin absorption. Rotate insulin injection or infusion sites within the same region to reduce the risk of lipodystrophy. [See *Dosage and Administration* (2.1)].

• *Weight gain*

Weight gain can occur with insulin therapy, including LANTUS, and has been attributed to the anabolic effects of insulin and the decrease in glucosuria.

• *Peripheral Edema*

Insulin, including LANTUS, may cause sodium retention and edema, particularly if previously poor metabolic control is improved by intensified insulin therapy.

• *Allergic Reactions*

Local Allergy

As with any insulin therapy, patients taking LANTUS may experience injection site reactions, including redness, pain, itching, urticaria, edema, and inflammation. In clinical studies in adult patients, there was a higher incidence of treatment-emergent injection site pain in LANTUS-treated patients (2.7%) compared to NPH insulin-treated patients (0.7%). The reports of pain at the injection site did not result in discontinuation of therapy.

Rotation of the injection site within a given area from one injection to the next may help to reduce or prevent these reactions. In some instances, these reactions may be related to factors other than insulin, such as irritants in a skin cleansing agent or poor injection technique. Most minor reactions to insulin usually resolve in a few days to a few weeks.

Systemic Allergy

Severe, life-threatening, generalized allergy, including anaphylaxis, generalized skin reactions, angioedema, bronchospasm, hypotension, and shock may occur with any insulin, including LANTUS and may be life threatening.

• *Antibody production*

All insulin products can elicit the formation of insulin antibodies. The presence of such insulin antibodies may increase or decrease the efficacy of insulin and may require adjustment of the insulin dose. In phase 3 clinical trials of LANTUS, increases in titers of antibodies to insulin were observed in NPH insulin and insulin glargine treatment groups with similar incidences.

6.2 Postmarketing experience

The following adverse reactions have been identified during post-approval use of LANTUS.

Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to estimate reliably their frequency or establish a causal relationship to drug exposure.

Medication errors have been reported in which other insulins, particularly short-acting insulins, have been accidentally administered instead of LANTUS [See *Patient Counseling Information* (17) in the full prescribing information]. To avoid medication errors between LANTUS and other insulins, patients should be instructed to always verify the insulin label before each injection.

7. DRUG INTERACTIONS

A number of drugs affect glucose metabolism and may require insulin dose adjustment and particularly close monitoring.

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

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

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-SA-SEP09

VITALS

Major Finding: For every 1 million people who receive the pandemic influenza vaccine, about 1 additional person will develop Guillain-Barré syndrome.

Data Source: A nationwide federal Guillain Barré Syndrome surveillance system.

Disclosures: None noted.

their health-care providers before receiving any influenza vaccine,” K.R. Copeland of the National Opinion Research Center, Chicago, and co-authors wrote in an accompanying editorial note. “However, risk assessment should take into account that influenza and influenza-like illnesses are associated with significant morbidity and mortality, including a hospitalization rate of 222 per 1 million population and a death rate of 9.7 per 1 million population for H1N1-associated illnesses, as well as possible increased risk for GBS.”

Of the 326 confirmed GBS cases, 27 had documentation proving pandemic flu vaccination within the 42-day window; vaccination status could not be determined in 25, and 274 were not vaccinated.

Sixteen of the 27 (59%) who received the vaccine experienced antecedent symptoms before their GBS diagnosis. The program found no clustering of GBS between vaccination and illness onset.

Among the 27 with GBS who were vaccinated, 4 (15%) required ventilator support, and 1 was hospitalized for 30 days. Among the 274 GBS patients who were not vaccinated, 37 (14%) required ventilator support, and 34 (12%) were hospitalized for 30 days after illness onset. Eight GBS patients died (2%); none of them had received the pandemic flu vaccine.

The CDC study used data gathered by its Emerging Infections Program. The program has collaborated with state health centers and academic medical centers in 10 states to rapidly identify new GBS cases following pandemic flu vaccination.

The surveillance areas included Connecticut, Maryland, Minnesota, New Mexico, Tennessee, and New York state (excluding Manhattan), and selected metropolitan counties in California, Colorado, Georgia, and Oregon. GBS incidence was calculated and compared for the vaccinated and unvaccinated populations. ■