

Think in Subcategories for Recalcitrant Obesity

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SAN DIEGO — Thinking of weight gain simply as the sum of “calories in minus calories out” doesn’t cover a minority of obese patients whose dietary records show reasonable caloric balance but who can’t seem to lose weight, Dr. Scott R. Rigden said.

These patients may show dietary records reflecting an intake of 1,800-1,900 calories per day, and often say they’re tired

of health care providers thinking that they’re lying in their food diaries because they haven’t lost weight, he said at a symposium on obesity sponsored by the American Society of Bariatric Physicians.

“I really think there are a lot of people with special issues, with switched-off metabolisms, that don’t fit that model” of calories in/calories out, said Dr. Rigden, a family physician in Chandler, Ariz. who also has practiced bariatrics since 1976. “What has shut down their metabolism,

and how do we turn it back on?”

To help these patients, think in terms of the following five subcategories, and tailor dietary and lifestyle recommendations accordingly, he suggested.

► **Carbohydrate sensitivity.** Dr. Rigden defined a patient with carbohydrate sensitivity as one whose genetic makeup produces a rapid spike of glucose after consuming simple carbohydrates and sugars. That glucose spike in turn triggers a spike in insulin and associated metabolic cellu-

lar messengers that tell the body to store fat, not burn it. The insulin spike also causes a rapid and uncomfortable drop in glucose that motivates the person to seek more carbohydrates and sugars to remedy the discomfort.

These patients do not yet meet criteria for metabolic syndrome. They have normal fasting insulin and glucose levels and are not hypertensive. “They often have stellar labs, yet a terrible lifelong obesity issue,” Dr. Rigden said. He has devised a nine-item questionnaire focusing on eating and exercise habits to identify this subgroup.

A four-step treatment plan starts with behavior modification to change the patient’s relationship with food and an exercise program with at least 150 minutes of moderate aerobic exercise weekly. The third step emphasizes adequate water intake of at least 64 ounces per day—“perhaps the most overlooked part of a weight management program,” he added.

Dietary intervention is the fourth step, starting with a soy protein powder meal replacement plan and switching to a low glycemic diet (which he also called a modified Mediterranean diet) after the patient loses 5%-10% of initial weight.

► **Metabolic syndrome.** Diagnostic criteria for metabolic syndrome include an elevated waist circumference, triglyceride level above 150 mg/dL, an HDL level less than 40 mg/dL for males or less than 50 mg/dL for females, blood pressure above 130/85 mmHg, and fasting blood sugar above 100 mg/dL.

In these patients, foods that have a high glycemic index cause blood sugar levels to plummet, boosting cravings for more high-glycemic foods such as sugars and fat, Dr. Rigden said. He recommends what he calls a “caveman or cavewoman” diet of low-fat, nonstarchy foods that he spells out for patients. After losing 10% of body weight, they switch to the low glycemic diet.

He also recommends nutraceutical medical food with slow-release, amylose-resistant starch, and soluble fiber in the form of 15 g per day of guar gum. Micronutrient support may be the most undervalued component of therapy for these patients, he added.

► **Hormonal imbalances.** Questionnaires and physical exams will help identify the endocrine problems contributing to recalcitrant obesity in these patients, Dr. Rigden said. Most will be due to clinical or subclinical hypothyroidism. “This is probably the No. 1 hormonal imbalance that I see in people who have switched metabolism,” he said.

Polycystic ovarian syndrome or a sex hormone imbalance with estrogen dominance are other problems to consider. Tailor treatment to the particular problem, he said.

► **Food hypersensitivity.** These are not true allergies but hypersensitivities that can lead to switched metabolism, Dr. Rigden said. Wheat and milk are the most common reactors, with delayed physical findings—such as boggy nasal mucosa or urticaria—appearing 24-72 hours after ingestion. IgG levels may help identify offending foods.

He said he has no conflict of interest with regard to the products he discussed. ■

Brief Summary of Prescribing Information April 2006

LANTUS®

(insulin glargine [rDNA origin] injection)

LANTUS® must NOT be diluted or mixed with any other insulin or solution.

INDICATIONS AND USAGE

LANTUS is indicated for once-daily subcutaneous administration for the treatment of adult and pediatric patients with type 1 diabetes mellitus or adult patients with type 2 diabetes mellitus who require basal (long-acting) insulin for the control of hyperglycemia.

CONTRAINDICATIONS

LANTUS is contraindicated in patients hypersensitive to insulin glargine or the excipients.

WARNINGS

Hypoglycemia is the most common adverse effect of insulin, including LANTUS. As with all insulins, the timing of hypoglycemia may differ among various insulin formulations. Glucose monitoring is recommended for all patients with diabetes.

Any change of insulin should be made cautiously and only under medical supervision. Changes in insulin strength, timing of dosing, manufacturer, type (e.g., regular, NPH, or insulin analogs), species (animal, human), or method of manufacture (recombinant DNA versus animal-source insulin) may result in the need for a change in dosage. Concomitant oral antidiabetes treatment may need to be adjusted.

PRECAUTIONS

General:

LANTUS is not intended for intravenous administration. The prolonged duration of activity of insulin glargine is dependent on injection into subcutaneous tissue. Intravenous administration of the usual subcutaneous dose could result in severe hypoglycemia.

LANTUS must NOT be diluted or mixed with any other insulin or solution. If LANTUS is diluted or mixed, the solution may become cloudy, and the pharmacokinetic/pharmacodynamic profile (e.g., onset of action, time to peak effect) of LANTUS and/or the mixed insulin may be altered in an unpredictable manner. When LANTUS and regular human insulin were mixed immediately before injection in dogs, a delayed onset of action and time to maximum effect for regular human insulin was observed. The total bioavailability of the mixture was also slightly decreased compared to separate injections of LANTUS and regular human insulin. The relevance of these observations in dogs to humans is not known.

As with all insulin preparations, the time course of LANTUS action may vary in different individuals or at different times in the same individual and the rate of absorption is dependent on blood supply, temperature, and physical activity. Insulin may cause sodium retention and edema, particularly if previously poor metabolic control is improved by intensified insulin therapy.

Hypoglycemia:

As with all insulin preparations, hypoglycemic reactions may be associated with the administration of LANTUS. Hypoglycemia is the most common adverse effect of insulins. Early warning symptoms of hypoglycemia may be different or less pronounced under certain conditions, such as long duration of diabetes, diabetes nerve disease, use of medications such as beta-blockers, or intensified diabetes control (see PRECAUTIONS, Drug Interactions). Such situations may result in severe hypoglycemia (and, possibly, loss of consciousness) prior to patients’ awareness of hypoglycemia.

The time of occurrence of hypoglycemia depends on the action profile of the insulins used and may, therefore, change when the treatment regimen or timing of dosing is changed. Patients being switched from twice daily NPH insulin to once-daily LANTUS should have their initial LANTUS dose reduced by 20% from the previous total daily NPH dose to reduce the risk of hypoglycemia (see DOSAGE AND ADMINISTRATION, Changeover to LANTUS).

The prolonged effect of subcutaneous LANTUS may delay recovery from hypoglycemia.

In a clinical study, symptoms of hypoglycemia or counterregulatory hormone responses were similar after intravenous insulin glargine and regular human insulin both in healthy subjects and patients with type 1 diabetes.

Renal Impairment:

Although studies have not been performed in patients with diabetes and renal impairment, LANTUS requirements may be diminished because of reduced insulin metabolism, similar to observations found with other insulins (see CLINICAL PHARMACOLOGY, Special Populations).

Hepatic Impairment:

Although studies have not been performed in patients with diabetes and hepatic impairment, LANTUS requirements may be diminished due to reduced capacity for gluconeogenesis and reduced insulin metabolism, similar to observations found with other insulins (see CLINICAL PHARMACOLOGY, Special Populations).

Injection Site and Allergic Reactions:

As with any insulin therapy, lipodystrophy may occur at the injection site and delay insulin absorption. Other injection site reactions with insulin therapy include redness, pain, itching, hives, swelling, and inflammation. Continuous rotation of the injection site within a given area may help to reduce or prevent these reactions. Most minor reactions to insulins usually resolve in a few days to a few weeks.

Reports of injection site pain were more frequent with LANTUS than NPH human insulin (2.7% insulin glargine versus 0.7% NPH). The reports of pain at the injection site were usually mild and did not result in discontinuation of therapy. Immediate-type allergic reactions are rare. Such reactions to insulin (including insulin glargine) or the excipients may, for example, be associated with generalized skin reactions, angioedema, bronchospasm, hypotension, or shock and may be life threatening.

Intercurrent Conditions:

Insulin requirements may be altered during intercurrent conditions such as illness, emotional disturbances, or stress.

Information for Patients:

LANTUS must only be used if the solution is clear and colorless with no particles visible (see DOSAGE AND ADMINISTRATION, Preparation and Handling).

Patients must be advised that LANTUS must NOT be diluted or mixed with any other insulin or solution (see PRECAUTIONS, General).

Patients should be instructed on self-management procedures including glucose monitoring, proper injection technique, and hypoglycemia and hyperglycemia management. Patients must be instructed on handling of special situations such as intercurrent conditions (illness, stress, or emotional disturbances), an inadequate or skipped insulin dose, inadvertent administration of an increased insulin dose, inadequate food intake, or skipped meals. Refer patients to the LANTUS “Patient Information” circular for additional information.

As with all patients who have diabetes, the ability to concentrate and/or react may be impaired as a result of hypoglycemia or hyperglycemia.

Patients with diabetes should be advised to inform their health care professional if they are pregnant or are contemplating pregnancy.

Drug Interactions:

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

The following are examples of substances that may increase the blood-glucose-lowering effect and susceptibility to hypoglycemia: oral antidiabetes products, ACE inhibitors, disopyramide, fibrates, fluoxetine, MAO inhibitors, propoxyphene, salicylates, somatostatin analog (e.g., octreotide), sulfonamide antibiotics.

The following are examples of substances that may reduce the blood-glucose-lowering effect of insulin: corticosteroids, danazol, diuretics, sympathomimetic agents (e.g., epinephrine, albuterol, terbutaline), 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.

In addition, under the influence of sympatholytic medicinal products such as beta-blockers, dionidine, guanethidine, and reserpine, the signs of hypoglycemia may be reduced or absent.

Carcinogenesis, Mutagenesis, Impairment of Fertility:

In mice and rats, standard two-year carcinogenicity studies with insulin glargine were performed at doses up to 0.455 mg/kg, which is for the rat approximately 10 times and for the mouse approximately 5 times the recommended human subcutaneous starting dose of 10 IU (0.008 mg/kg/day), based on mg/m². The findings in female mice were not conclusive due to excessive mortality in all dose groups during the study. Histiocytomas were found at injection sites in male rats (statistically significant) and male mice (not statistically significant) in acid vehicle containing groups. These tumors were not found in female animals, in saline control, or insulin comparator groups using a different vehicle. The relevance of these findings to humans is unknown.

Insulin glargine was not mutagenic in tests for detection of gene mutations in bacteria and mammalian cells (Ames- and HGPRT-tests) and in tests for detection of chromosomal aberrations (cytogenetics in vitro in V79 cells and in vivo in Chinese hamsters).

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In a combined fertility and prenatal and postnatal study in male and female rats at subcutaneous doses up to 0.36 mg/kg/day, which is approximately 7 times the recommended human subcutaneous starting dose of 10 IU (0.008 mg/kg/day), based on mg/m², maternal toxicity due to dose-dependent hypoglycemia, including some deaths, was observed. Consequently, a reduction of the rearing rate occurred in the high-dose group only. Similar effects were observed with NPH human insulin.

Pregnancy:

Teratogenic Effects: Pregnancy Category C. Subcutaneous reproduction and teratology studies have been performed with insulin glargine and regular human insulin in rats and Himalayan rabbits. The drug 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 IU (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 IU (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 insulin glargine in pregnant women. 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 such patients. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers:

It is unknown whether insulin glargine is excreted in significant amounts in human milk. Many drugs, including human insulin, are excreted in human milk. For this reason, caution should be exercised when LANTUS is administered to a nursing woman. Lactating women may require adjustments in insulin dose and diet.

Pediatric Use:

Safety and effectiveness of LANTUS have been established in the age group 6 to 15 years with type 1 diabetes.

Geriatric Use:

In controlled clinical studies comparing insulin glargine to NPH human insulin, 593 of 3890 patients with type 1 and type 2 diabetes were 65 years and older. The only difference in safety or effectiveness in this subpopulation compared to the entire study population was an expected higher incidence of cardiovascular events in both insulin glargine and NPH human insulin-treated 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 PRECAUTIONS, Hypoglycemia).

ADVERSE REACTIONS

The adverse events commonly associated with LANTUS include the following:

Body as a whole: allergic reactions (see PRECAUTIONS).

Skin and appendages: injection site reaction, lipodystrophy, pruritus, rash (see PRECAUTIONS).

Other: hypoglycemia (see WARNINGS and PRECAUTIONS).

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 were usually mild and did not result in discontinuation of therapy. Other treatment-emergent injection site reactions occurred at similar incidences with both insulin glargine and NPH human insulin.

Retinopathy was evaluated in the clinical studies by means of retinal adverse events reported and fundus photography. The numbers of retinal adverse events reported for LANTUS and NPH treatment groups were similar for patients with type 1 and type 2 diabetes. Progression of retinopathy was investigated by fundus photography using a grading protocol derived from the Early Treatment Diabetic Retinopathy Study (ETDRS). In one clinical study involving patients with type 2 diabetes, a difference in the number of subjects with ≥3-step progression in ETDRS scale over a 6-month period was noted by fundus photography (7.5% in LANTUS group versus 2.7% in NPH treated group). The overall relevance of this isolated finding cannot be determined due to the small number of patients involved, the short follow-up period, and the fact that this finding was not observed in other clinical studies.

OVERDOSAGE

An excess of insulin relative to food intake, energy expenditure, or both may lead to severe and sometimes long-term 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 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.

DOSAGE AND ADMINISTRATION

LANTUS is a recombinant human insulin analog. Its potency is approximately the same as human insulin. It exhibits a relatively constant glucose-lowering profile over 24 hours that permits once-daily dosing.

LANTUS may be administered at any time during the day. LANTUS should be administered subcutaneously once a day at the same time every day. For patients adjusting timing of dosing with LANTUS, see **WARNINGS and PRECAUTIONS, Hypoglycemia**. LANTUS is not intended for intravenous administration (see PRECAUTIONS). Intravenous administration of the usual subcutaneous dose could result in severe hypoglycemia. The desired blood glucose levels as well as the doses and timing of antidiabetes medications must be determined individually. Blood glucose monitoring is recommended for all patients with diabetes. The prolonged duration of activity of LANTUS is dependent on injection into subcutaneous space. As with all insulins, injection sites within an injection area (abdomen, thigh, or deltoid) must be rotated from one injection to the next.

In clinical studies, there was no relevant difference in insulin glargine absorption after abdominal, deltoid, or thigh subcutaneous administration. As for all insulins, the rate of absorption, and consequently the onset and duration of action, may be affected by exercise and other variables.

LANTUS is not the insulin of choice for the treatment of diabetes ketoacidosis. Intravenous short-acting insulin is the preferred treatment.

Pediatric Use:

LANTUS can be safely administered to pediatric patients ≥6 years of age. Administration to pediatric patients <6 years has not been studied. Based on the results of a study in pediatric patients, the dose recommendation for changeover to LANTUS is the same as described for adults in DOSAGE AND ADMINISTRATION, Changeover to LANTUS.

Initiation of LANTUS Therapy:

In a clinical study with insulin naïve patients with type 2 diabetes already treated with oral antidiabetes drugs, LANTUS was started at an average dose of 10 IU once daily, and subsequently adjusted according to the patient’s need to a total daily dose ranging from 2 to 100 IU.

Changeover to LANTUS:

If changing from a treatment regimen with an intermediate- or long-acting insulin to a regimen with LANTUS, the amount and timing of short-acting insulin or fast-acting insulin analog or the dose of any oral antidiabetes drug may need to be adjusted. In clinical studies, when patients were transferred from once-daily NPH human insulin or ultralente human insulin to once-daily LANTUS, the initial dose was usually not changed. However, when patients were transferred from twice-daily NPH human insulin to LANTUS once daily, to reduce the risk of hypoglycemia, the initial dose (IU) was usually reduced by approximately 20% (compared to total daily IU of NPH human insulin) and then adjusted based on patient response (see PRECAUTIONS, Hypoglycemia).

A program of dose metabolic monitoring under medical supervision is recommended during transfer and in the initial weeks thereafter. The amount and timing of short-acting insulin or fast-acting insulin analog may need to be adjusted. This is particularly true for patients with acquired antibodies to human insulin needing high-insulin doses and occurs with all insulin analogs. Dose adjustment of LANTUS and other insulins or oral antidiabetes drugs may be required; for example, if the patient’s timing of dosing, weight or lifestyle changes, or other circumstances arise that increase susceptibility to hypoglycemia or hyperglycemia (see PRECAUTIONS, Hypoglycemia).

The dose may also have to be adjusted during intercurrent illness (see PRECAUTIONS, Intercurrent Conditions).

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