Annual High-Dose Vit. D Raises Fall, Break Risks

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Far from protecting older women from falls and fractures, yearly high-dose oral vitamin D raised the risk of falls by 15% and that of fractures by 26%, according to an Australian study.

These risks were highest in the 3-month period immediately after each annual dose, said Kerrie M. Sanders, Ph.D., of the University of Melbourne and her associates.

As this study used the "largest total annual dose of vitamin D (500,000 IU) reported in any large randomized controlled trial," it is possible that these adverse outcomes are related to the dosage, or perhaps to the once-a-year regimen. But the levels of 25-hydroxycholecalciferol achieved in these subjects can also occur with other dosing regimens, so it appears that the safety of all high-dose vitamin D supplementation warrants further examination, they noted.

Dr. Sanders and her colleagues performed their single-center study in 2,256 white women aged at least 70. They were considered at risk for hip fracture because of their family or personal histories or because they reported recent falls.

The subjects were randomly assigned to receive a single oral dose of vitamin D (cholecalciferol) or a matching placebo at the same time every year for 3-5 years. Lab studies in a subgroup of the subjects showed that the active treatment raised levels of 25-hydroxycholecalciferol an average of 41%, as expected.

There were 5,404 falls during follow-up, involving 74% of the women taking vitamin D and 68% of those taking placebo. The rate of falls was 83 per 100 person-years with vitamin D, compared

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

Brief Summary of Prescribing Information

1. INDICATIONS AND USAGE
LANTUS is indicated to improve glycemic control in adults and children with type 1 diabetes mellitus and in adults with type 2 diabetes mellitus.
Important Limitations of Use:
- LANTUS is not recommended for the treatment of diabetic ketoacidosis. Intravenous short-acting insulin is the preferred treatment for this condition.

2. DOSAGE AND ADMINISTRATION
2.1 Dosing
LANTUS is a recombinant human insulin analog for once daily subcutaneous administration with potency that is approximately the same as the potency of human insulin. LANTUS 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. The dose of LANTUS must be individualized based on clinical response. Blood glucose monitoring is essential in all patients receiving insulin therapy.
Patients adjusting the amount or timing of dosing with LANTUS, should only do so under medical supervision with appropriate glucose monitoring *[see Warnings and Precautions (5.1).*]
In patients with type 1 diabetes, LANTUS must be used in regimens with short-acting insulin.
The intended duration of activity of LANTUS is dependent on injection into subcutaneous tissue *[see Clinical pharmacology (12.2) in the full prescribing information]*. LANTUS should not be administered intravenously or via an insulin pump. Intravenous administration of the usual subcutaneous dose could result in severe hypoglycemia *[see Warnings and Precautions (5.3)]*.
As with all insulins, injection sites should be rotated within the same region (abdomen, thigh, or deltoid) from one injection to the next to reduce the risk of lipodystrophy *[See Adverse Reactions (6.1)]*.
In clinical studies, there was no clinically 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, such as stress, intercurrent illness, or changes in co-administered drugs or meal patterns.
2.2 Initiation of LANTUS therapy
The recommended starting dose of LANTUS in patients with type 1 diabetes should be approximately one-third of the total daily insulin requirements. Short-acting, premeal insulin should be used to satisfy the remainder of the daily insulin requirements.
The recommended starting dose of LANTUS in patients with type 2 diabetes who are not currently treated with insulin is 10 units (or 0.2 Units/kg) once daily, which should subsequently be adjusted to the patient's needs.
The dose of LANTUS should be adjusted according to blood glucose measurements. The dosage of LANTUS should be individualized under the supervision of a healthcare provider in accordance with the needs of the patient.
2.3 Converting to LANTUS from other insulin therapies
If changing from a treatment regimen with an intermediate- or long-acting insulin to a regimen with LANTUS, the amount and timing of shorter-acting insulins and doses of any oral anti-diabetic drugs may need to be adjusted.
- If transferring patients from once-daily NPH insulin to once-daily LANTUS, the recommended initial LANTUS dose is the same as the dose of NPH that is being discontinued.
- If transferring patients from twice-daily NPH insulin to once-daily LANTUS, the recommended initial LANTUS dose is 80% of the total NPH dose that is being discontinued. This dose reduction will lower the likelihood of hypoglycemia [*see Warnings and Precautions (5.3)].*

4. CONTRAINDICATIONS
LANTUS is contraindicated in patients with hypersensitivity to LANTUS or one of its excipients.
5. WARNINGS AND PRECAUTIONS
5.1 Dosage adjustment and monitoring
Glucose monitoring is essential for all patients receiving insulin therapy. Changes to an insulin regimen should be made cautiously and only under medical supervision.
Changes in insulin strength, manufacturer, type, or method of administration may result in the need for a change in insulin dose or an adjustment in concomitant oral anti-diabetic treatment.
As with all insulin preparations, the time course of action for LANTUS may vary in different individuals or at different times in the same individual and is dependent on many conditions, including the local blood supply, local temperature, and physical activity.
5.2 Administration
Do not administer LANTUS intravenously or via an insulin pump. The intended duration of activity of LANTUS is dependent on injection into subcutaneous tissue
Intravenous administration of the usual subcutaneous dose could result in severe hypoglycemia *[see Warnings and Precautions (5.3)]*.
Do not dilute or mix LANTUS with any other insulin or solution. If LANTUS is diluted or mixed, the solution may become cloudy, and the pharmacokinetic or pharmacodynamic profile (e.g., onset of action, time to peak effect) of LANTUS and 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 a delayed 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 unknown.
Do not share disposable or reusable insulin devices or needles between patients, because doing so carries a risk for transmission of blood-borne pathogens.
5.3 Hypoglycemia
Hypoglycemia is the most common adverse reaction of insulin, including LANTUS. The risk of hypoglycemia increases with intensive glycemic control. Patients must be educated to recognize and manage hypoglycemia. Severe hypoglycemia can lead to unconsciousness or convulsions and may result in temporary or permanent impairment of brain function or death. Severe hypoglycemia requiring the assistance of another person or parenteral glucose infusion or glucagon administration has been observed in clinical trials with insulin, including trials with LANTUS.
The timing of hypoglycemia usually reflects the time-action profile of the administered insulin formulations. Other factors such as changes in food intake (e.g., amount of food or timing of meals), exercise, and concomitant medications may also alter the risk of hypoglycemia [*See Drug Interactions (7)*].
The prolonged effect of subcutaneous LANTUS may delay recovery from hypoglycemia. 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 (2.3)]*.
As with all insulins, use caution in patients with hypoglycemia unawareness and in patients who may be predisposed to hypoglycemia (e.g., the pediatric population and patients who fast or have erratic food intake). The patient's ability to concentrate and react may be impaired as a result of hypoglycemia. This may present a risk in situations where these abilities are especially important, such as driving or operating other machinery.
Early warning symptoms of hypoglycemia may be different or less pronounced under certain conditions, such as longstanding diabetes, diabetic neuropathy, use of medications such as beta-blockers, or intensified glycemic control. These situations may result in severe hypoglycemia (and, possibly, loss of consciousness) prior to the patient's awareness of hypoglycemia.
5.4 Hypersensitivity and allergic reactions
Severe, life-threatening, generalized allergy, including anaphylaxis, can occur with insulin products, including LANTUS.
5.5 Renal impairment
Due to its long duration of action, Lantus is not recommended during periods of rapidly declining renal function because of the risk for prolonged hypoglycemia.
Although studies have not been performed in patients with diabetes and renal impairment, a reduction in the LANTUS dose may be required in patients with renal impairment because of reduced insulin metabolism, similar to observations found with other insulins. *[See Clinical Pharmacology (12.3) in the full prescribing information].*
5.6 Hepatic impairment
Due to its long duration of action, Lantus is not recommended during periods of rapidly declining hepatic function because of the risk for prolonged hypoglycemia.
Although studies have not been performed in patients with diabetes and hepatic impairment, a reduction in the LANTUS dose may be required in patients with hepatic impairment because of reduced capacity for gluconeogenesis and reduced insulin metabolism, similar to observations found with other insulins. *[See Clinical Pharmacology (12.3) in the full prescribing information].*
5.7 Drug interactions
Some medications may alter insulin requirements and subsequently increase the risk for hypoglycemia or hyperglycemia *[See Drug Interactions (7)]*.
6. ADVERSE REACTIONS
The following adverse reactions are discussed elsewhere:
- Hypoglycemia *[See Warnings and Precautions (5.3)]*
- Hypersensitivity and allergic reactions *[See Warnings and Precautions (5.4)]*

6.1 Clinical trial experience
Because clinical trials are conducted under widely varying designs, the adverse reaction rates reported in one clinical trial may not be easily compared to those rates reported in another clinical trial, and may not reflect the rates actually observed in clinical practice.
The frequencies of treatment-emergent adverse events during LANTUS clinical trials in patients with type 1 diabetes mellitus and type 2 diabetes mellitus are listed in the tables below.

Table 1: Treatment –emergent adverse events in pooled clinical trials up to 28 weeks duration in adults with type 1 diabetes (adverse events with frequency ≥ 5%)

	LANTUS, % (n=1257)	NPH, % (n=1070)
Upper respiratory tract infection	22.4	23.1
Infection *	9.4	10.3

with 73 per 100 person-years with placebo, a statistically significant difference.

The increase in falls with active treatment was noted in falls that produced fractures and those that didn't, and in falls that produced soft-tissue injury.

A total of 155 women taking vitamin D sustained 171 fractures during follow-up, compared with 125 women taking placebo who sustained 135 fractures. This translates to a rate of 4.9 fractures per 100 person-years with active treatment and 3.9 fractures per 100 person-years with placebo.

These risks of falls and of fractures did not change after the data were adjusted to account for subjects' calcium intake.

"Contrary to our hypothesis, participants receiving annual high-dose oral cholecalciferol experienced 15% more falls and 26% more fractures than [did] the placebo group. Women not only experienced excess fractures after more frequent falls but also experienced more fractures that were not associated with a fall," the investigators noted (JAMA 2010;303:1815-22).

The reason for these counterproductive effects is not yet known, but it is possible that the once-a-year oral regimen—compared with either a regimen that divides the oral doses or one that uses intramuscular doses—is at fault. "It is reasonable to speculate that high serum levels of vitamin D or metabolites resulting from the large annual dose, subsequent decrease in the levels, or both might be causal," they wrote.

In an accompanying editorial, Dr. Bess Dawson-Hughes and Susan S. Harris, D.Sc., of the Jean Mayer USDA Human Nutrition Research Center on Aging at Tufts University, Boston, said that these study findings should not detract from the importance of "correcting widespread vitamin D deficiency and insufficiency.

"There is no evidence for adverse effects of more frequent, lower-dose regimens, so daily, weekly, or monthly dosing with vitamin D_3 appears to be the best option for clinicians at this time," they noted (JAMA 2010;303:1861-2). ■

Disclosures: *This study was supported by the National Health and Medical Research Council and the Australian Government Department of Health and Ageing. No conflicts of interest were reported by Dr. Sanders and her associates, Dr. Dawson-Hughes, or Dr. Harris.*

Table 1: Treatment –emergent adverse events in pooled clinical trials up to 28 weeks duration in adults with type 1 diabetes (adverse events with frequency ≥ 5%) (continued)

	LANTUS, % (n=1257)	NPH, % (n=1070)
Accidental injury	5.7	6.4
Headache	5.5	4.7

*Body System not Specified

Table 2: Treatment –emergent adverse events in pooled clinical trials up to 1 year duration in adults with type 2 diabetes (adverse events with frequency ≥ 5%)

	LANTUS, % (n=849)	NPH, % (n=714)
Upper respiratory tract infection	11.4	13.3
Infection*	10.4	11.6
Retinal vascular disorder	5.8	7.4

*Body System not Specified

Table 3: Treatment –emergent adverse events in a 5-year trial of adults with type 2 diabetes (adverse events with frequency ≥ 10%)

	LANTUS, % (n=514)	NPH, % (n=503)
Upper respiratory tract infection	29.0	33.6
Edema peripheral	20.0	22.7
Hypertension	19.6	18.9
Influenza	18.7	19.5
Sinusitis	18.5	17.9
Cataract	18.1	15.9
Bronchitis	15.2	14.1
Arthralgia	14.2	16.1
Pain in extremity	13.0	13.1
Back pain	12.8	12.3
Cough	12.1	7.4
Urinary tract infection	10.7	10.1
Diarrhea	10.7	10.3
Depression	10.5	9.7
Headache	10.3	9.3

Table 4: Treatment –emergent adverse events in a 28-week clinical trial of children and adolescents with type 1 diabetes (adverse events with frequency ≥ 5%)

	LANTUS, % (n=174)	NPH, % (n=175)
Infection*	13.8	17.7
Upper respiratory tract infection	13.8	16.0
Pharyngitis	7.5	8.6
Rhinitis	5.2	5.1

*Body System not Specified

• *Severe Hypoglycemia*

Hypoglycemia is the most commonly observed adverse reaction in patients using insulin, including LANTUS *[See Warnings and Precautions (5.3)]*. Tables 5 and 6 summarize the incidence of severe hypoglycemia in the LANTUS individual clinical trials. Severe symptomatic hypoglycemia was defined as an event with symptoms consistent with hypoglycemia requiring the assistance of another person and associated with either a blood glucose below 50 mg/dL (≤56 mg/dL in the 5-year

trial) or prompt recovery after oral carbohydrate, intravenous glucose or glucagon administration.

The rates of severe symptomatic hypoglycemia in the LANTUS clinical trials (see Section 14 in the full prescribing information for a description of the study designs) were comparable for all treatment regimens (see Tables 5 and 6). In the pediatric phase 3 clinical trial, children and adolescents with type 1 diabetes had a higher incidence of severe symptomatic hypoglycemia in the two treatment groups compared to the adult trials with type 1 diabetes. (see Table 5) *[See Clinical Studies (14) in the full prescribing information].*

Table 5: Severe Symptomatic Hypoglycemia in Patients with Type 1 Diabetes

	Study A Type 1 Diabetes Adults 28 weeks In combination with regular insulin		Study B Type 1 Diabetes Adults 28 weeks In combination with regular insulin		Study C Type 1 Diabetes Adults 16 weeks In combination with insulin lispro		Study D Type 1 Diabetes Pediatrics 26 weeks In combination with regular insulin	
	LANTUS	NPH	LANTUS	NPH	LANTUS	NPH	LANTUS	NPH
Percent of patients (n/total N)	10.6 (31/292)	15.0 (44/293)	8.7 (23/264)	10.4 (28/270)	6.5 (20/310)	5.2 (16/309)	23.0 (40/174)	28.6 (50/175)

Table 6: Severe Symptomatic Hypoglycemia in Patients with Type 2 Diabetes

	Study E Type 2 Diabetes Adults 52 weeks In combination with oral agents		Study F Type 2 Diabetes Adults 28 weeks In combination with regular insulin		Study G Type 2 Diabetes Adults 5 years In combination with regular insulin	
	LANTUS	NPH	LANTUS	NPH	LANTUS	NPH
Percent of patients (n/total N)	1.7 (5/289)	1.1 (3/281)	0.4 (1/259)	2.3 (6/259)	7.8 (40/513)	11.9 (60/504)

• *Retinopathy*

Retinopathy was evaluated in the LANTUS clinical studies by analysis of reported retinal adverse events and fundus photography. The numbers of retinal adverse events reported for LANTUS and NPH insulin treatment groups were similar for patients with type 1 and type 2 diabetes.

LANTUS was compared to NPH insulin in a 5-year randomized clinical trial that evaluated the progression of retinopathy as assessed with fundus photography using a grading protocol derived from the Early Treatment Diabetic Retinopathy Scale (ETDRS). Patients had type 2 diabetes (mean age 55 yrs) with no (86%) or mild (14%) retinopathy at baseline. Mean baseline HbA1c was 8.4%. The primary outcome was progression by 3 or more steps on the ETDRS scale at study endpoint. Patients with pre-specified post-baseline eye procedures (pan-retinal photocoagulation for proliferative or severe nonproliferative diabetic retinopathy, local photocoagulation for new vessels, and vitrectomy for diabetic retinopathy) were also considered as 3-step progressors regardless of actual change in ETDRS score from baseline. Retinopathy graders were blinded to treatment group assignment. The results for the primary endpoint are shown in Table 7 for both the per-protocol and Intent-to-Treat populations, and indicate similarity of Lantus to NPH in the progression of diabetic retinopathy as assessed by this outcome.

Table 7. Number (%) of patients with 3 or more step progression on ETDRS scale at endpoint

	Lantus (%)	NPH (%)	Difference*,† (SE)	95% CI for difference
Per-protocol	53/374 (14.2%)	57/363 (15.7%)	-2.0% (2.6%)	-7.0% to +3.1%
Intent-to-Treat	63/502 (12.5%)	71/487 (14.6%)	- 2.1% (2.1%)	-6.3% to +2.1%

*Difference = Lantus – NPH

†using a generalized linear model (SAS GENMOD) with treatment and baseline HbA1c strata (cutoff 9.0%) as the classified independent variables, and with binomial distribution and identity link function