Adding Alcohol to Diet Lowers Glucose in Type 2

BY MIRIAM E. TUCKER
Senior Writer

AMSTERDAM — Initiation of moderate daily alcohol consumption among patients with type 2 diabetes results in decreased fasting plasma glucose levels, particularly among patients with worse control at baseline, Iris Shai, Ph.D., reported at the annual meeting of the European Association for the Study of Diabetes.

Alcohol may inhibit hepatic glucose production—as does metformin—and also has been associated with beneficial cardiovascular effects. A recent meta-analysis of observational studies suggested that moderate alcohol consumption is associated with a reduced risk of coronary heart disease mortality among patients with type 2 diabetes, and that the beneficial association is greater than among nondiabetics (Diabetologia 2006;49:648-52).

But although several short-term intervention studies have found a decrease in fasting plasma glucose (FPG) levels in diabetic patients with moderate alcohol intake, other studies have not, said Dr. Shai, of the Ben-Gurion University of the Negev, Beer-Sheva, Israel.

A randomized, controlled intervention study to investigate the association was jointly sponsored by the Israeli Diabetes Research Group; Harvard University; the Tishbi Estate Winery, Israel; and Admiral Imports, Cedar Grove, N.J. A total of 109 initially nondrinking (defined as one drink or less per week) patients with type 2 diabetes aged 40-75 years were randomized to either 150 cc of wine (13 g alcohol, 100 kcal) or the same amount of nonalcoholic diet malt beer (0 g alcohol, 30 kcal) during dinner, both served in the same standard measured glass. The wine group could choose either dry red (merlot) or white (sauvignon blanc), said Dr. Shai, who is also a registered dietician.

Participants met with the nurse study coordinator eight times during the trial and with physicians and dieticians at weeks 1, 7, and 12. All study participants received individual dietary counseling, including identical nutritional strategies to achieve glycemic control without aiming for dramatic weight loss. Both groups were instructed to reduce their carbohydrate intake at breakfast and/or lunch but not at dinner, the wine group by 100 kcal and the controls by 30 kcal. Prior to each visit, the subjects filled in 3-day diaries of their food and drink consumption.

A total of 201 patients were screened, of whom 126 were eligible, 109 were randomized, and 91 completed the study. Dropouts were higher among the control group (26% vs. 12% of the intervention group). "Most were disappointed not to be assigned to the wine group," Dr. Shai said. The dropouts had significantly higher baseline FPG levels, she noted.

At baseline, the 61 men and 48 women who were randomized ranged in age from 41 to 74 years, had an average FPG of 144.5 mg/dL, a hemoglobin A_{1c} (HbA_{1c}) level of 7.39%, blood pressure of 133.7/76.5 mm Hg, and body mass index of 30.1 kg/m^2. After 3 months, the alcohol group experienced a significant 9.2% decrease in FPG, from 139.6 to 118.0 mg/dL. Patients with the highest baseline HbA_{1c} values experienced the greatest declines in FPG following moderate alcohol consumption. There was no change in FPG in the control group.

In contrast to the FPG, there were nonsignificant increases in 2-hour postmeal glucose levels, based on an average of self-measurements. Within the alcohol group, there were significant decreases in HbA_{1c} (from 7.37% to 7.07%), LDL cholesterol (96.65 to 85.11 mg/dL), and waist circumference, but not in HDL cholesterol. These changes did not differ significantly between the two groups, however, she said. (HbA_{1c} values dropped slightly in the controls, from 7.08% to 6.84%.)

Liver function biomarkers—including bilirubin, alkaline phosphatases, ALT, and AST—did not change significantly at 12 weeks in either group, although there was a "hint" of an increase in ALT (from 23.17 to 32.92 U/L) and AST (21.15 to 30.47 U/L) in the intervention group. In a long list of side effects to choose from, both groups reported feeling more "calm" after the study. The only effect checked off significantly more often by the alcohol group was an improved ability to fall asleep, Dr. Shai said.

At 6 months after the beginning of the study (3 months after its termination), 61% of the alcohol group thought that the alcohol was beneficial to them, and 49% were continuing to drink alcohol in moderation, ranging from one drink a week to one a day. ■

Levemir®
insulin detemir (rDNA origin) injection

Rx ONLY
BRIEF SUMMARY. Please see package insert for prescribing information.

INDICATIONS AND USAGE
LEVEMIR is indicated for once- or twice-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
LEVEMIR is contraindicated in patients hypersensitive to insulin detemir or one of its excipients.

WARNINGS
Hypoglycemia is the most common adverse effect of insulin therapy, including LEVEMIR. As with all insulins, the timing of hypoglycemia may differ among various insulin formulations.

Glucose monitoring is recommended for all patients with diabetes.

LEVEMIR is not to be used in insulin infusion pumps.

Any change of insulin dose 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 (rDNA versus animal-source insulin) may result in the need for a change in dosage. Concomitant oral antidiabetic treatment may need to be adjusted.

PRECAUTIONS
General
Inadequate dosing or discontinuation of treatment may lead to hyperglycemia and, in patients with type 1 diabetes, diabetic ketoacidosis. The first symptoms of hyperglycemia usually occur gradually over a period of hours or days. They include nausea, vomiting, drowsiness, flushed dry skin, dry mouth, increased urination, thirst and loss of appetite as well as acetone breath. Untreated hyperglycemic events are potentially fatal.

LEVEMIR is not intended for intravenous or intramuscular administration. The prolonged duration of activity of insulin detemir is dependent on injection into subcutaneous tissue. Intravenous administration of the usual subcutaneous dose could result in severe hypoglycemia. Absorption after intramuscular administration is both faster and more extensive than absorption after subcutaneous administration.

LEVEMIR should not be diluted or mixed with any other insulin preparations (see PRECAUTIONS, Mixing of Insulins).

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

Lipodystrophy and hypersensitivity are among potential clinical adverse effects associated with the use of all insulins.

As with all insulin preparations, the time course of LEVEMIR action may vary in different individuals or at different times in the same individual and is dependent on site of injection, blood supply, temperature, and physical activity.

Adjustment of dosage of any insulin may be necessary if patients change their physical activity or their usual meal plan.

Hypoglycemia
As with all insulin preparations, hypoglycemic reactions may be associated with the administration of LEVEMIR. 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, diabetic 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. In patients being switched from other intermediate or long-acting insulin preparations to once- or twice-daily LEVEMIR, dosages can be prescribed on a unit-to-unit basis; however, as with all insulin preparations, dose and timing of administration may need to be adjusted to reduce the risk of hypoglycemia.

Renal Impairment
As with other insulins, the requirements for LEVEMIR may need to be adjusted in patients with renal impairment.

Hepatic Impairment
As with other insulins, the requirements for LEVEMIR may need to be adjusted in patients with hepatic impairment.

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 may 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. Reactions usually resolve in a few days to a few weeks. On rare occasions, injection site reactions may require discontinuation of LEVEMIR.

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.

Systemic allergy: Generalized allergy to insulin, which is less common but potentially more serious, may cause rash (including pruritus) over the whole body, shortness of breath, wheezing, reduction in blood pressure, rapid pulse, or sweating. Severe cases of generalized allergy, including anaphylactic reaction, may be life-threatening.

Intercurrent Conditions
Insulin requirements may be altered during intercurrent conditions such as illness, emotional disturbances, or other stresses.

Information for Patients
LEVEMIR must only be used if the solution appears clear and colorless with no visible particles. Patients should be informed about potential risks and advantages of LEVEMIR therapy, including the possible side effects. Patients should be offered continued education and advice on insulin therapies, injection technique, life-style management, regular glucose monitoring, periodic glycosylated hemoglobin testing, recognition and management of hypo- and hyperglycemia, adherence to meal planning, complications of insulin therapy, timing of dosage, instruction for use of injection devices and proper storage of insulin. Patients should be informed that frequent, patient-performed blood glucose measurements are needed to achieve effective glycemic control to avoid both hyperglycemia and hypoglycemia. 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 LEVEMIR "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 (see PRECAUTIONS, Pregnancy).

Laboratory Tests
As with all insulin therapy, the therapeutic response to LEVEMIR should be monitored by periodic blood glucose tests. Periodic measurement of HbA_{1c} is recommended for the monitoring of long-term glycemic control.

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 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).

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

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, clonidine, guanethidine, and reserpine, the signs of hypoglycemia may be reduced or absent.

The results of *in-vitro* and *in-vivo* protein binding studies demonstrate that there is no clinically relevant interaction between insulin detemir and fatty acids or other protein bound drugs.

Mixing of Insulins
If LEVEMIR is mixed with other insulin preparations, the profile of action of one or both individual components may change. Mixing LEVEMIR with insulin aspart, a rapid acting insulin analog, resulted in about 40% reduction in $AUC_{(0\text{-}2h)}$ and C_{max} for insulin aspart compared to separate injections when the ratio of insulin aspart to LEVEMIR was less than 50%.

LEVEMIR should NOT be mixed or diluted with any other insulin preparations.

Carcinogenicity, Mutagenicity, Impairment of Fertility
Standard 2-year carcinogenicity studies in animals have not been performed. Insulin detemir tested negative for genotoxic potential in the *in-vitro* reverse mutation study in bacteria, human peripheral blood lymphocyte chromosome aberration test, and the *in-vivo* mouse micronucleus test.

Pregnancy: Teratogenic Effects: Pregnancy Category C
In a fertility and embryonic development study, insulin detemir was administered to female rats before mating, during mating, and throughout pregnancy at doses up to 300 nmol/kg/day (3 times the recommended human dose, based on plasma Area Under the Curve (AUC) ratio). Doses of 150 and 300 nmol/kg/day produced numbers of litters with visceral anomalies. Doses up to 900 nmol/kg/day (approximately 135 times the recommended human dose based on AUC ratio) were given to rabbits during organogenesis. Drug-dose related increases in the incidence of fetuses with gall bladder abnormalities such as small, bilobed, bifurcated and missing gall bladders were observed at a dose of 900 nmol/kg/day. The rat and rabbit embryofetal development studies that included concurrent human insulin control groups indicated that insulin detemir and human insulin had similar effects regarding embryotoxicity and teratogenicity.

Nursing mothers
It is unknown whether LEVEMIR is excreted in significant amounts in human milk. For this reason, caution should be exercised when LEVEMIR is administered to a nursing mother. Patients with diabetes who are lactating may require adjustments in insulin dose, meal plan, or both.

Pediatric use
In a controlled clinical study, HbA_{1c} concentrations and rates of hypoglycemia were similar among patients treated with LEVEMIR and patients treated with NPH human insulin.

Geriatric use
Of the total number of subjects in intermediate and long-term clinical studies of LEVEMIR, 85 (type 1 studies) and 363 (type 2 studies) were 65 years and older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. 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.

ADVERSE REACTIONS
Adverse events commonly associated with human insulin therapy include the following:

Body as Whole: allergic reactions (see PRECAUTIONS, Allergy).

Skin and Appendages: lipodystrophy, pruritus, rash. Mild injection site reactions occurred more frequently with LEVEMIR than with NPH human insulin and usually resolved in a few days to a few weeks (see PRECAUTIONS, Allergy).

Other:

Hypoglycemia: (see WARNINGS and PRECAUTIONS).

In trials of up to 6 months duration in patients with type 1 and type 2 diabetes, the incidence of severe hypoglycemia with LEVEMIR was comparable to the incidence with NPH, and, as expected, greater overall in patients with type 1 diabetes (Table 4).

Weight gain:
In trials of up to 6 months duration in patients with type 1 and type 2 diabetes, LEVEMIR was associated with somewhat less weight gain than NPH (Table 4). Whether these observed differences represent true differences in the effects of LEVEMIR and NPH insulin is not known, since these trials were not blinded and the protocols (e.g., diet and exercise instructions and monitoring) were not specifically directed at exploring hypotheses related to weight effects of the treatments compared. The clinical significance of the observed differences has not been established.

Table 4: Safety Information on Clinical Studies

			Weight (kg)		Hypoglycemia (events/subject/month)	
	Treatment	# of subjects	Baseline	End of treatment	Major*	Minor**
Type 1						
Study A	LEVEMIR	N=276	75.0	75.1	0.045	2.184
	NPH	N=133	75.7	76.4	0.035	3.063
Study C	LEVEMIR	N=492	76.5	76.3	0.029	2.397
	NPH	N=257	76.1	76.5	0.027	2.564
Study D	LEVEMIR	N=232	N/A	N/A	0.076	2.677
Pediatric	NPH	N=115	N/A	N/A	0.083	3.203
Type 2						
Study E	LEVEMIR	N=237	82.7	83.7	0.001	0.306
	NPH	N=239	82.4	85.2	0.006	0.595
Study F	LEVEMIR	N=195	81.8	82.3	0.003	0.193
	NPH	N=200	79.6	80.9	0.006	0.235

* Major = requires assistance of another individual because of neurologic impairment
** Minor = plasma glucose <56 mg/dl, subject able to deal with the episode him/herself

OVERDOSAGE
Hypoglycemia may occur as a result of an excess of insulin relative to food intake, energy expenditure, or both. Mild episodes of hypoglycemia usually can be treated with oral glucose. 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 reoccurrence of hypoglycemia.

More detailed information is available on request.

Rx only

Date of issue: October 19, 2005

Manufactured for Novo Nordisk Inc., Princeton, NJ 08540

Manufactured by Novo Nordisk A/S, 2880 Bagsvaerd, Denmark

www.novonordisk-us.com

Levemir® and Novo Nordisk® are trademarks of Novo Nordisk A/S.

© 2006 Novo Nordisk Inc. 130128R May 2006

novo nordisk®