Repeat Measurements Unveil Masked Hypertension

BY CAROLINE HELWICK Contributing Writer

NEW ORLEANS — "Masked hypertension," which is thought to affect about one in eight individuals, can be identified through repeated office blood pressure measurements in persons who show discrepancy between office and home blood pressure levels, according to Italian investigators.

"We were able to diagnose masked hy-

pertension by using repeated office measurements. It matches what our patients found in home monitoring,"reported principal investigator Dr. Giuseppe Crippa of Guglielmo da Saliceto Hospital, Piacenza, Italy.

Masked hypertension is defined as normal office blood pressure but high ambulatory blood pressure or home blood pressure. It is estimated that the condition is as prevalent as white-coat hypertension and is often missed in clinical practice, Dr. Crippa explained at the annual meeting of the American Society of Hypertension.

His study compared the level of agreement between office blood pressure (OBP), repeated office blood pressure (ROBP), and daytime ambulatory blood pressure (ABP) in 48 patients pharmacologically untreated with subjects with normal office blood pressure (less than 140/90 mm Hg) but elevated daytime ABP (at least 135/85 mm Hg).

Since ABP averages multiple measure-

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 concentrations and rates o 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 LEVENIR, 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 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 maintenanc dosage should be conservative to avoid hypoglycemic reaction 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, LEVENIR was associated with somewhat less weight gain than NPH (Table 4). Whether these observed differences represent true differences in the effects of LEVENIR 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 Hypoglycemia (events/subject/month Baseline End of Major* Minor Treatment Type 1 N=276 75.0 75.1 LEVEMIR 0.045 2.184 Study A N=133 0.035 3.063 NPH 75.7 76.4

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

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

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ments, it is the accepted standard for diagnosing masked hypertension. For follow-up, home blood pressure measurement is regarded as a simpler, reliable, and cost-effective alternative, he said.

OBP values were derived from the average of at least three sphygmomanometric measurements obtained during at least three separate visits, over a 3-week period. ABP values were calculated as the average of daytime readings taken every 15 minutes and nighttime readings obtained every 30 minutes. ROBP was performed after 20 minutes of rest with the patient seated comfortably alone; 10 consecutive measurements were taken every 2.5 minutes, with the average of the final

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six readings considered the final value. This is impor-

tant, Dr. Crippa noted, because the average blood pressure varies highly over 20 consecutive measurements. For example, in one patient, the initial reading taken at 8:02 a.m.

was 210/121 mm Hg and pulse rate was 96 beats per minute (bpm); midway through the ROBP it dropped to 140/79 mm Hg and 80 bpm; and concluded at 137/77 mm Hg and 72 bpm. Over the 20 readings, the average of the first 4 was 185/106 mm Hg, while the average of the final 6 readings was 138/77 mm Hg.

In the study, the OBP readings (both systolic and diastolic) were slightly but significantly lower than those achieved with ABP or ROBP.

The differences between OBP and both ABP and ROBP were statistically significant. The ABP and ROBP readings were not significantly different and, in fact, were highly correlated with each other, Dr. Crippa reported.

With ABP as a reference for the diagnosis of masked hypertension, ROBP failed to identify this condition in just 2 out of the 48 patients.

"According to our results, ROBP seems to provide reliable information on blood pressure status that compares favorably with the most precise and exhaustive technique for the diagnosis of masked hypertension, that is, [ambulatory blood pressure monitoring]," Dr. Crippa explained. "In a population of untreated subjects, ROBP and ABP monitoring provided a very similar proportion of individuals with masked hypertension, and the level of agreement, for the same subject, was more than acceptable. The precision and power of detection by ROBP seems very high, with an attractive cost/efficacy ratio."

The majority of subjects (94% according to ABP monitoring values) had OBP values in the prehypertensive range, he added, suggesting that masked hypertension might be regarded as a high-risk subset of prehypertension.



insulin detemir (rDNA origin) injection

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

INDICATIONS AND USAGE

VDICATIONS AND USAGE EVEMIR is indicated for once- or twice-daily subcutaneous diministration for the treatment of adult and pediatric patients vith type 1 diabetes mellitus or adult patients with type 2 iabetes mellitus who require basal (long acting) insulin for the ported of byperclycemia diabe

control of hyperglycemia

CONTRAINDICATIONS LEVENIR 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 Levenink is not to be used in insulin intusion 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 manufacturer (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

Inadequate dosing or discontinuation of treatment may lead to 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.

Untreated nypergivernic 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 it eviously 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

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.

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 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.

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 agen 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 he life-thestening. cases of generalized be life-threatening.

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

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, hypoglycema. Patients must be instructed on handling of special situations such as intercurrent conditions (liness, 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 informat

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 HbA₁ 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 incre-the blood-glucose-lowering effect of insulin and suscep-to hypoglycemia: oral antidiabetic drugs, ACE inhibitor, disopyramide, fibrates, fluoxetine, MAO inhibitors, prop otibility rs, propoxyphene salicylates, somatostatin analog (e.g., octreotide), and sulfonamide antibiotics.

Beta-blockers, clonidine, lithium salts, and alcohol m 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 bet insulin detemir and fatty acids or other protein bound drugs. action hotwoor

Mixing of Insulins If LEVEMIR is mixed with other insulin preparations, the profi 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_(0.2h) and C_{max} arraiog, resulted in about 40% reduction in AUC_(0.2h) and C_{ma} 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 deternir 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

rregnancy: leratogenic Liftects: Pregnancy Category C In a fertility and embryonic development study, insulin determir 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 niven to rabits churing 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