

Fish Oil Fails to Cut Arrhythmias in SOFA Trial

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STOCKHOLM — Fish-oil supplements did not significantly reduce the incidence of life-threatening ventricular arrhythmias in high-risk patients in a large, double-blind, randomized European trial, Ingeborg A. Brouwer, Ph.D., said at the annual congress of the European Society of Cardiology.

Results of the Study on Omega-3 Fatty Acids and Ventricular Arrhythmia (SOFA)

were disappointing in view of the great need for broad new approaches to reducing the risk of sudden arrhythmic death in the general population.

Implantable cardioverter defibrillators (ICDs) are highly effective but serve a relatively small number of the highest-risk patients; the great majority of sudden deaths occur in individuals who will never be candidates for such devices. The published literature had held out the promise that increased intake of fish oil might be an easy,

safe, and effective means of reducing risk in the general population, explained Dr. Brouwer of the Wageningen (the Netherlands) Center for Food Sciences.

SOFA did not completely shut the door on fish oil as an antiarrhythmic agent, however. In a subgroup analysis confined to participants with prior MI, there was a strong, albeit nonsignificant, trend toward a beneficial effect worthy of further investigation, she added.

SOFA was a 26-center double-blind tri-

al involving 546 ICD wearers in eight European countries who were randomized to 2 g/day of fish oil or placebo for 1 year. Patients with ICDs were chosen for the study because the device memory provides detailed information on all arrhythmic episodes.

After 1 year of follow-up, the rate of the combined end point of all-cause mortality or life-threatening ventricular arrhythmia was 33% in the control group and 30% in the fish-oil group, a nonsignificant difference. The difference between the two groups in time to a first life-threatening arrhythmic episode was also nonsignificant.

However, in the 342 patients with a history of MI, the rate of the composite end point was 35% with placebo and 28% in the fish-oil group—not a statistically significant difference, but encouraging, Dr. Brouwer continued.

SOFA was the second negative randomized trial of fish oil in ICD patients in recent months. Earlier, investigators at Oregon Health and Science University, Portland, reported on 200 patients with an ICD who were randomized to 1.8 g/day of fish oil or placebo in a double-blind,



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DR. BROUWER

multicenter trial. During 2 years of follow-up, 65% of patients in the fish-oil group experienced one or more appropriate ICD firings to terminate a life-threatening ventricular arrhythmia, a rate not significantly different from the 59% figure among controls (JAMA 2005;293:2884-91).

Discussant Luigi Tavazzi, M.D., said there is another randomized trial of fish oil in patients with ICDs, this one not yet published but strongly positive. The one consistent finding in all of these studies is that fish oil is safe. Much larger than all three studies put together, however, is the ongoing Italian Group for the Study of Cardiac Insufficiency Survival (GISSI)-HF study, in which more than 7,000 patients with chronic heart failure have been randomized to fish oil or placebo, and those eligible for statin therapy have been randomized to 10 mg/day of rosiglitazone or placebo. Follow-up is planned for 3 years, with results anticipated in late 2007.

GISSI-HF was undertaken because of the provocative results of the earlier GISSI-Prevention trial. In this landmark study, more than 11,300 patients were randomized to daily fish oil and/or vitamin E beginning not more than 3 months after an MI. Vitamin E was found to have no benefit. However, during 3.5 years of follow-up, fish oil was associated with a 30% reduction in risk of cardiovascular death and a 44% reduction in sudden death (Lancet 1999;354:447-55).

SOFA was sponsored by the Wageningen Center, with additional support from the European Union. ■

HUMALOG® Mix75/25™ 75% INSULIN LISPRO PROTAMINE SUSPENSION AND 25% INSULIN LISPRO INJECTION (rDNA ORIGIN)

BRIEF SUMMARY: Consult the package insert for complete prescribing information.

INDICATIONS AND USAGE: Humalog® Mix75/25, a mixture of 75% insulin lispro protamine suspension and 25% insulin lispro, is indicated in the treatment of patients with diabetes mellitus for the control of hyperglycemia. Humalog Mix75/25 has a more rapid onset of glucose-lowering activity compared with Humulin 70/30 while having a similar duration of action. This profile is achieved by combining the rapid onset of Humalog with the intermediate action of insulin lispro protamine suspension.

CONTRAINDICATIONS: Humalog Mix75/25 is contraindicated during episodes of hypoglycemia and in patients sensitive to insulin lispro or any of the excipients contained in the formulation.

WARNINGS: Humalog differs from regular human insulin by its rapid onset of action as well as a shorter duration of activity. Therefore, the dose of Humalog Mix75/25 should be given within 15 minutes before a meal.

Hypoglycemia is the most common adverse effect associated with the use of insulins, including Humalog Mix75/25. 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, manufacturer, type (e.g., regular, NPH, analog), species (animal, human), or method of manufacture (rDNA versus animal-source insulin) may result in the need for a change in dosage.

PRECAUTIONS: *General*—Hypoglycemia and hypokalemia are among the potential clinical adverse effects associated with the use of all insulins. Because of differences in the action of Humalog Mix75/25 and other insulins, care should be taken in patients in whom such potential side effects might be clinically relevant (e.g., patients who are fasting, have autonomic neuropathy, or are using potassium lowering drugs or patients taking drugs sensitive to serum potassium level). Lipodystrophy and hypersensitivity are among other potential clinical adverse effects associated with the use of all insulins.

As with all insulin preparations, the time course of action of Humalog Mix75/25 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. Insulin requirements may be altered during illness, emotional disturbances, or other stress.

Hypoglycemia—As with all insulin preparations, hypoglycemic reactions may be associated with the administration of Humalog Mix75/25. Rapid changes in serum glucose concentrations may induce symptoms of hypoglycemia in persons with diabetes, regardless of the glucose value. 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.

Renal Impairment—As with other insulins, the requirements for Humalog Mix75/25 may be reduced in patients with renal impairment.

Hepatic Impairment—Although impaired hepatic function does not affect the absorption or disposition of Humalog, careful glucose monitoring and dose adjustments of insulin, including Humalog Mix75/25, may be necessary.

Allergy—Local Allergy—As with any insulin therapy, patients may experience redness, swelling, or itching at the site of injection. These minor reactions usually resolve in a few days to a few weeks. In some instances, these reactions may be related to factors other than insulin, such as irritants in the skin cleansing agent or poor injection technique.

Systemic Allergy—Less common, but potentially more serious, is generalized allergy to insulin, which 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. Localized reactions and generalized myalgias have been reported with the use of cresol as an injectable excipient.

Antibody Production—In clinical trials, antibodies that cross react with human insulin and insulin lispro were observed in both human insulin mixtures and insulin lispro mixtures treatment groups.

Information for Patients—Patients should be informed of the potential risks and advantages of Humalog Mix75/25 and alternative therapies. Patients should not mix Humalog Mix75/25 with any other insulin. They should also be informed about the importance of proper insulin storage, injection technique, timing of dosage, adherence to meal planning, regular physical activity, regular blood glucose monitoring, periodic glycosylated hemoglobin testing, recognition and management of hypo- and hyperglycemia, and periodic assessment for diabetes complications.

Patients should be advised to inform their physician if they are pregnant or intend to become pregnant.

Refer patients to the "INFORMATION FOR THE PATIENT" insert for information on normal appearance, proper resuspension and injection techniques, timing of dosing (within 15 minutes before a meal), storing, and common adverse effects.

Laboratory Tests—As with all insulins, the therapeutic response to Humalog Mix75/25 should be monitored by periodic blood glucose tests. Periodic measurement of glycosylated hemoglobin is recommended for the monitoring of long-term glycemic control.

Drug Interactions—Insulin requirements may be increased by medications with hyperglycemic activity such as corticosteroids, isoniazid, certain lipid-lowering drugs (e.g., niacin), estrogens, oral contraceptives, phenothiazines, and thyroid replacement therapy.

Insulin requirements may be decreased in the presence of drugs with hypoglycemic activity, such as oral antidiabetic agents, salicylates, sulfa antibiotics, certain antidepressants (monoamine oxidase inhibitors), certain angiotensin-converting-enzyme inhibitors, beta-adrenergic blockers, inhibitors of pancreatic function (e.g., octreotide), and alcohol. Beta-adrenergic blockers may mask the symptoms of hypoglycemia in some patients.

Carcinogenesis, Mutagenesis, Impairment of Fertility—Long-term studies in animals have not been performed to evaluate the carcinogenic potential of Humalog or Humalog

Mix75/25. Insulin lispro was not mutagenic in a battery of *in vitro* and *in vivo* genetic toxicity assays (bacterial mutation tests, unscheduled DNA synthesis, mouse lymphoma assay, chromosomal aberration tests, and a micronucleus test). There is no evidence from animal studies of impairment of fertility induced by insulin lispro.

Pregnancy—Teratogenic Effects—Pregnancy Category B—Reproduction studies with insulin lispro have been performed in pregnant rats and rabbits at parenteral doses up to 4 and 0.3 times, respectively, the average human dose (40 units/day) based on body surface area. The results have revealed no evidence of impaired fertility or harm to the fetus due to insulin lispro. There are, however, no adequate and well controlled studies with Humalog or Humalog Mix75/25 in pregnant women. 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 lispro 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 Humalog Mix75/25 is administered to a nursing woman. Patients with diabetes who are lactating may require adjustments in Humalog Mix75/25 dose, meal plan, or both.

Pediatric Use—Safety and effectiveness of Humalog Mix75/25 in patients less than 18 years of age have not been established.

Geriatric Use—Clinical studies of Humalog Mix75/25 did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently than younger patients. In general, dose selection for an elderly patient should take into consideration the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy in this population.

ADVERSE REACTIONS: Clinical studies comparing Humalog Mix75/25 with human insulin mixtures did not demonstrate a difference in frequency of adverse events between the two treatments.

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

Body as a Whole—allergic reactions (see PRECAUTIONS).

Skin and Appendages—injection site reaction, lipodystrophy, pruritus, rash.

Other—hypoglycemia (see WARNINGS and PRECAUTIONS).

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. Sustained carbohydrate intake and observation may be necessary because hypoglycemia may recur after apparent clinical recovery.

DOSAGE AND ADMINISTRATION: Humalog Mix75/25 is intended only for subcutaneous administration. Humalog Mix75/25 should not be administered intravenously. Dosage regimens of Humalog Mix75/25 will vary among patients and should be determined by the Health Care Professional familiar with the patient's metabolic needs, eating habits, and other lifestyle variables. Humalog has been shown to be equipotent to regular human insulin on a molar basis. One unit of Humalog has the same glucose lowering effect as one unit of regular human insulin, but its effect is more rapid and of shorter duration. Humalog Mix75/25 has a similar glucose lowering effect as compared with Humulin 70/30 on a unit for unit basis. The quicker glucose-lowering effect of Humalog is related to the more rapid absorption rate of insulin lispro from subcutaneous tissue.

Humalog Mix75/25 starts lowering blood glucose more quickly than regular human insulin, allowing for convenient dosing immediately before a meal (within 15 minutes). In contrast, mixtures containing regular human insulin should be given 30 to 60 minutes before a meal.

The rate of insulin absorption and consequently the onset of activity are known to be affected by the site of injection, exercise, and other variables. As with all insulin preparations, the time course of action of Humalog Mix75/25 may vary considerably in different individuals or within the same individual. Patients must be educated to use proper injection techniques.

Humalog Mix75/25 should be inspected visually before use. Humalog Mix75/25 should be used only if it appears uniformly cloudy after mixing. Humalog Mix75/25 should not be used after its expiration date.

HOW SUPPLIED: Humalog Mix75/25 vials are available in the following package size:

100 units per mL (U 100)
10 mL vials
NDC 0002 7511 01 (VL 7511)

Humalog Mix75/25 Pen, a disposable insulin delivery device, is available in the following package size:

5 x 3 mL disposable insulin delivery devices
NDC 0002 8794 59 (HP 8794)

Storage—Humalog Mix75/25 should be stored in a refrigerator (36° to 46°F [2° to 8°C]), but not in the freezer. Do not use Humalog Mix75/25 if it has been frozen. Unrefrigerated (below 86°F [30°C]) vials must be used within 28 days or be discarded, even if they still contain Humalog Mix75/25. Unrefrigerated (below 86°F [30°C]) Pens must be used within 10 days or be discarded, even if they still contain Humalog Mix75/25. Protect Humalog Mix75/25 vials or Pens from direct heat and light.

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PV 4841 AMP

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