Treatment Falling Short for Many GERD Patients

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MONTREAL — Gastroesophageal reflux symptoms are poorly controlled across North America and Europe, and people with nocturnal symptoms represent the largest treatment gap, according to two different industry-sponsored studies presented in a series of posters at the 12th World Congress of Gastroenterology.

"There's a huge unmet prescribing need," said Farah Husein-Bhabha, from Janssen-Ortho Inc. in Toronto, which sponsored one of the studies. "We found that the use of over-the-counter drugs is much higher than prescription drug use, and yet these patients continue to experience symptoms," she told FAMILY PRACTICE NEWS.

The Canadian study randomly polled 2,001 individuals by telephone to assess the prevalence and impact of gastroesophageal reflux disease (GERD) in the general population.

Just over 40% of the respondents (820) reported at least one upper gastrointestinal symptom in the last month, with the most common complaint being GERD (367). Among GERD sufferers, 54% had sought medical help for their problem, while 46% had not.

The U.S./European study (sponsored by AstraZeneca) which randomly polled a much larger sample of about 212,000 households, identified 1,908 respondents who were either formally diagnosed (52%) or undiagnosed but with symptoms suggestive of GERD (48%).

Both studies identified a high percentage (64% and 50%, respectively) of patients who reported nocturnal GERD symptoms either alone, or together with daytime symptoms.

In the Canadian study, 47% of those with nocturnal symptoms reported disturbed sleep, and 43% of these people reported a negative impact on their daytime functioning and productivity as a result.

The U.S./European study found that, when woken up with GERD symptoms, people stayed awake an average of 70 minutes and missed an average of 30 minutes of work per week as a result. This compared with only 6 minutes of lost work time per week in GERD patients without disturbed sleep. GERD-related sleep disturbance was estimated to be responsible for a 15% reduction in work productivity and a 14% reduction in leisure time, compared with an 8% and 10% reduction in GERD patients without disturbed sleep.

Nocturnal GERD symptoms are of particular concern not only for quality of life reasons, but also because of their long-term implications, said Ms. Husein-Bhabha.

"If a patient has nocturnal symptoms, it generally means a more severe type of GERD, and there may also be an association with more erosive disease. There is a certain percentage of the population that may progress to esophageal cancer if they are untreated. But for many patients who do not have erosive disease that risk is small and probably less than we had originally thought."

Both studies found that GERD symptoms are undertreated.

In the Canadian population, 57% of GERD sufferers were taking over-the-counter (OTC) medications, while 25% used prescription medications. In the U.S./European study, 74% of the diagnosed group were taking prescription medications (55% of which were proton pump inhibitors), while 85% of the undiagnosed group were taking OTC medications.

Despite some improvement resulting from these treatments, the majority of patients in the U.S./European study reported unresolved symptoms (81% of the self-treated group and 68% of those taking prescription medications).

In the Canadian study, only 54% of patients using proton pump inhibitors (PPI) for nocturnal relief felt satisfied with the treatment.

"Our findings imply the use of medication for management of GERD can be improved," concluded the authors of the U.S./European study. "Symptoms were more likely to improve when GERD was formally diagnosed by a physician and PPIs prescribed… Individuals with persistent GERD symptoms should consult a physician."

The Canadian study found that the strongest predictor of a person seeking GERD treatment from a physician was nocturnal GERD that disrupted sleep. Other predictors were older age, more severe symptoms, and longer duration of symptoms. ■

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*—Hypoglcemia 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 xcipients.

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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