

Botox May Reduce Frequency of Migraines

BY MICHELE G. SULLIVAN

PHILADELPHIA — OnabotulinumtoxinA appears to be a safe, effective, and well-tolerated headache prophylactic for patients with chronic migraine.

Two large randomized, controlled trials showed that the toxin significantly reduced migraine frequency and improved headache-related disability over 24 weeks, Dr. David W. Dodick reported at

the International Headache Congress.

The studies—PREEMPT 1 and 2—were conducted at 22 centers in North America and Europe, and included 1,384 patients (average age 41 years). Each trial consisted of a 4-week baseline period, during which patients kept a daily headache diary, followed by 24 weeks of treatment during which patients received two injection cycles of either placebo or onabotulinumtoxinA (Botox), which has

not been approved by the Food and Drug Administration for migraine prophylaxis. From 24 to 56 weeks, there was an open-label trial consisting of three injection cycles of the study drug, said Dr. Dodick of the Mayo Clinic Arizona, Phoenix.

At baseline, patients reported a mean of 20 headache days per month, 19 of which were considered migraine days, with a mean of 290 cumulative headache

hours. The mean score on the Headache Impact Test-6 (HIT-6) survey was 65, indicating severe impact. Most of the patients (93%) also reported severe headache-related disability, and 65% were overusing acute pain medications.

During the double-blind phase, patients randomized to the treatment group received two injection cycles (one every 12 weeks) of onabotulinumtoxinA 155 U. The medication was injected at 31 sites across seven muscle areas in the head and neck. At the physicians' discretion, an additional 40 U could be injected among three additional muscle groups; the maximum dose was 195 U.

The study's main end point was frequency of headache days; secondary end points were frequency of migraine days, moderate/severe headache days, monthly headache hours, and proportion of patients with a severe HIT-6 score.

At 24 weeks, patients in the active group had a significantly greater reduction in headache days and migraine days than those taking placebo (−8 vs. −6, respectively). The HIT-6 score also de-



Patients in the active group had a significantly greater reduction in migraine days than those taking placebo.

DR. DODICK

clined significantly more among the active group (−5 vs. −2 points). Patients receiving the study drug experienced a greater decrease in cumulative headache hours per month (−120 vs. −80 hours), and a lower proportion had a severe score on the HIT-6 survey (68% vs. 78%).

"The only outcome that was not statistically significantly better among the active group than the placebo group was the percentage overusing acute pain medications. However, the use of triptans did decrease significantly in the active group, compared to the placebo group," Dr. Dodick said at the congress, which was sponsored by the International Headache Society and the American Headache Society.

Adverse events occurred in 62% of those taking the study drug and 52% of those taking placebo—a significant difference. There were also significantly more treatment-related adverse events in the onabotulinumtoxinA group (29% vs. 13%). One serious treatment-related adverse event did occur in the active group—a severe postinjection migraine that required hospitalization. Adverse events occurring in more than 5% of the entire study group were neck pain (9%) and upper respiratory infection (5%). Four patients in the active group and one in the placebo group discontinued active injections because of an adverse event.

The study was sponsored by Allergan Inc., manufacturer of the study drug. Dr. Dodick reported having received honoraria from the company. ■

Reference: 1. IMS Health Inc. National Sales Perspectives (12 months ending December 2008).

NovoLog® (insulin aspart [rDNA origin] injection)

Rx only

BRIEF SUMMARY. Please consult package insert for full prescribing information.

INDICATIONS AND USAGE: NovoLog® is an insulin analog indicated to improve glycemic control in adults and children with diabetes mellitus.

CONTRAINDICATIONS: NovoLog® is contraindicated during episodes of hypoglycemia and in patients hypersensitive to NovoLog® or one of its excipients.

WARNINGS AND PRECAUTIONS: Administration: NovoLog® has a more rapid onset of action and a shorter duration of activity than regular human insulin. An injection of NovoLog® should immediately be followed by a meal within 5-10 minutes. Because of NovoLog®'s short duration of action, a longer acting insulin should also be used in patients with type 1 diabetes and may also be needed in patients with type 2 diabetes. Glucose monitoring is recommended for all patients with diabetes and is particularly important for patients using external pump infusion therapy. Any change of insulin dose should be made cautiously and only under medical supervision. Changing from one insulin product to another or changing the insulin strength may result in the need for a change in dosage. As with all insulin preparations, the time course of NovoLog® action may vary in different individuals or at different times in the same individual and is dependent on many conditions, including the site of injection, local blood supply, temperature, and physical activity. Patients who change their level of physical activity or meal plan may require adjustment of insulin dosages. Insulin requirements may be altered during illness, emotional disturbances, or other stresses. Patients using continuous subcutaneous insulin infusion pump therapy must be trained to administer insulin by injection and have alternate insulin therapy available in case of pump failure.

Hypoglycemia: Hypoglycemia is the most common adverse effect of all insulin therapies, including NovoLog®. Severe hypoglycemia may lead to unconsciousness and/or convulsions and may result in temporary or permanent impairment of brain function or death. Severe hypoglycemia requiring the assistance of another person and/or parenteral glucose infusion or glucagon administration has been observed in clinical trials with insulin, including trials with NovoLog®. The timing of hypoglycemia usually reflects the time-action profile of the administered insulin formulations [see *Clinical Pharmacology*]. Other factors such as changes in food intake (e.g., amount of food or timing of meals), injection site, exercise, and concomitant medications may also alter the risk of hypoglycemia [see *Drug Interactions*]. As with all insulins, use caution in patients with hypoglycemia unawareness and in patients who may be predisposed to hypoglycemia (e.g., patients who are fasting 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. Rapid changes in serum glucose levels 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 longstanding diabetes, diabetic nerve disease, use of medications such as beta-blockers, or intensified diabetes control [see *Drug Interactions*]. These situations may result in severe hypoglycemia (and, possibly, loss of consciousness) prior to the patient's awareness of hypoglycemia. Intravenously administered insulin has a more rapid onset of action than subcutaneously administered insulin, requiring more close monitoring for hypoglycemia. **Hypokalemia:** All insulin products, including NovoLog®, cause a shift in potassium from the extracellular to intracellular space, possibly leading to hypokalemia that, if left untreated, may cause respiratory paralysis, ventricular arrhythmia, and death. Use caution in patients who may be at risk for hypokalemia (e.g., patients using potassium-lowering medications, patients taking medications sensitive to serum potassium concentrations, and patients receiving intravenously administered insulin). **Renal Impairment:** As with other insulins, the dose requirements for NovoLog® may be reduced in patients with renal impairment [see *Clinical Pharmacology*]. **Hepatic Impairment:** As with other insulins, the dose requirements for NovoLog® may be reduced in patients with hepatic impairment [see *Clinical Pharmacology*]. **Hypersensitivity and Allergic Reactions: Local Reactions** - As with other insulin therapy, patients may experience redness, swelling, or itching at the site of NovoLog® injection. These reactions usually resolve in a few days to a few weeks, but in some occasions, may require discontinuation of NovoLog®. 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. Localized reactions and generalized myalgias have been reported with injected metacresol, which is an excipient in NovoLog®.

Systemic Reactions - Severe, life-threatening, generalized allergy, including anaphylaxis, may occur with any insulin product, including NovoLog®. Anaphylactic reactions with NovoLog® have been reported post-approval. Generalized allergy to insulin may also cause whole body rash (including pruritus), dyspnea, wheezing, hypotension, tachycardia, or diaphoresis. In controlled clinical trials, allergic reactions were reported in 3 of 735 patients (0.4%) treated with regular human insulin and 10 of 1394 patients (0.7%) treated with NovoLog®. In controlled and uncontrolled clinical trials, 3 of 2341 (0.1%) NovoLog®-treated patients discontinued due to allergic reactions. **Antibody Production:** Increases in anti-insulin antibody titers that react with both human insulin and insulin aspart have been observed in patients treated with NovoLog®. Increases in anti-insulin antibodies are observed more frequently with NovoLog® than with regular human insulin. Data from a 12-month controlled trial in patients with type 1 diabetes suggest that the increase in these antibodies is transient, and the differences in antibody levels between the regular human insulin and insulin aspart treatment groups observed at 3 and 6 months were no longer evident at 12 months. The clinical significance of these antibodies is not known. These antibodies do not appear to cause deterioration in glycemic control or necessitate increases in insulin dose. **Mixing of Insulins:** Mixing NovoLog® with NPH human insulin immediately before injection attenuates the peak concentration of NovoLog®, without significantly affecting the time to peak concentration or total bioavailability of NovoLog®. If NovoLog® is mixed with NPH human insulin, NovoLog® should be drawn into the syringe first, and the mixture should be injected immediately after mixing. The efficacy and safety of mixing NovoLog® with insulin preparations produced by other manufacturers have not been studied. Insulin mixtures should not be administered intravenously. **Subcutaneous continuous insulin infusion by external pump: When used in an external subcutaneous insulin infusion pump, NovoLog® should not be mixed with any other insulin or diluent.** When using NovoLog® in an external insulin pump, the NovoLog®-specific information should be followed (e.g., in-use time, frequency of changing infusion sets) because NovoLog®-specific information may differ from general pump manual instructions. Pump or infusion set malfunctions or insulin degradation can lead to a rapid onset of hyperglycemia and ketosis because of the small subcutaneous depot of insulin. This is especially pertinent for rapid-acting insulin analogs that are more rapidly absorbed through skin and have a shorter duration of action. Prompt identification and correction of the cause of hyperglycemia or ketosis is necessary. Interim therapy with subcutaneous injection may be required [see *Dosage and Administration, Warnings and Precautions, How Supplied/Storage and Handling, and Patient Counseling Information*]. NovoLog® is recommended for use in pump systems suitable for insulin infusion as listed below. **Pumps:** MiniMed 500 series and other equivalent pumps. **Reservoirs and infusion sets:** NovoLog® is recommended for use in reservoir and infusion sets that are compatible with insulin and the specific pump. In-vitro studies

have shown that pump malfunction, loss of metacresol, and insulin degradation, may occur when NovoLog® is maintained in a pump system for longer than 48 hours. Reservoirs and infusion sets should be changed at least every 48 hours. NovoLog® should not be exposed to temperatures greater than 37°C (98.6°F). **NovoLog® that will be used in a pump should not be mixed with other insulin or with a diluent** [see *Dosage and Administration, Warnings and Precautions and How Supplied/Storage and Handling, Patient Counseling Information*].

ADVERSE REACTIONS: 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. **Hypoglycemia:** Hypoglycemia is the most commonly observed adverse reaction in patients using insulin, including NovoLog® [see *Warnings and Precautions*]. **Insulin initiation and glucose control intensification:** Intensification or rapid improvement in glucose control has been associated with a transitory, reversible ophthalmologic refraction disorder, worsening of diabetic retinopathy, and acute painful peripheral neuropathy. However, long-term glycemic control decreases the risk of diabetic retinopathy and neuropathy. **Lipodystrophy:** Long-term use of insulin, including NovoLog®, can cause lipodystrophy at the site of repeated insulin injections or infusion. Lipodystrophy includes lipohypertrophy (thickening of adipose tissue) and lipatrophy (thinning of adipose tissue), and may affect insulin absorption. Rotate insulin injection or infusion sites within the same region to reduce the risk of lipodystrophy. **Weight gain:** Weight gain can occur with some insulin therapies, including NovoLog®, and has been attributed to the anabolic effects of insulin and the decrease in glucosuria. **Peripheral Edema:** Insulin may cause sodium retention and edema, particularly if previously poor metabolic control is improved by intensified insulin therapy. **Frequencies of adverse drug reactions:** The frequencies of adverse drug reactions during NovoLog® 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 Patients with Type 1 Diabetes Mellitus (Adverse events with frequency ≥ 5% and occurring more frequently with NovoLog® compared to human regular insulin are listed)

Preferred Term	NovoLog® + NPH N=596		Human Regular Insulin + NPH N=286	
	N	(%)	N	(%)
Hypoglycemia*	448	75%	205	72%
Headache	70	12%	28	10%
Injury accidental	65	11%	29	10%
Nausea	43	7%	13	5%
Diarrhea	28	5%	9	3%

*Hypoglycemia is defined as an episode of blood glucose concentration <45 mg/dL with or without symptoms. See *Clinical Studies* for the incidence of serious hypoglycemia in the individual clinical trials.

Table 2: Treatment-Emergent Adverse Events in Patients with Type 2 Diabetes Mellitus (except for hypoglycemia, adverse events with frequency ≥ 5% and occurring more frequently with NovoLog® compared to human regular insulin are listed)

	NovoLog® + NPH N=91		Human Regular Insulin + NPH N=91	
	N	(%)	N	(%)
Hypoglycemia*	25	27%	33	36%
Hyporeflexia	10	11%	6	7%
Onychomycosis	9	10%	5	5%
Sensory disturbance	8	9%	6	7%
Urinary tract infection	7	8%	6	7%
Chest pain	5	5%	3	3%
Headache	5	5%	3	3%
Skin disorder	5	5%	2	2%
Abdominal pain	5	5%	1	1%
Sinusitis	5	5%	1	1%

*Hypoglycemia is defined as an episode of blood glucose concentration <45 mg/dL, with or without symptoms. See *Clinical Studies* for the incidence of serious hypoglycemia in the individual clinical trials.

Postmarketing Data: The following additional adverse reactions have been identified during postapproval use of NovoLog®. Because these adverse reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency. Medication errors in which other insulins have been accidentally substituted for NovoLog® have been identified during postapproval use [see *Patient Counseling Information*].

OVERDOSAGE: Excess insulin administration may cause hypoglycemia and, particularly when given intravenously, hypokalemia. 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. Hypokalemia must be corrected appropriately.

More detailed information is available on request.

Date of Issue: March 14, 2008

Version 14

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

Manufactured for Novo Nordisk Inc., Princeton, New Jersey 08540

www.novonordisk-us.com

NovoLog® is a registered trademark of Novo Nordisk A/S.

NovoLog® is covered by US Patent Nos 5,618,913; 5,866,538; and other patents pending.

© 2008 Novo Nordisk Inc. 134600 4/08



NovoLog®
insulin aspart (rDNA origin) injection