Amitriptyline Overused in Elderly Neuropathy Patients

BY COLIN NELSON
Contributing Writer

BOSTON — Doctors continue to prescribe the antidepressant amitriptyline for treatment of diabetic peripheral neuropathy in the elderly despite advisories that discourage its use in this population, according to study findings reported at the annual meeting of the American Pain Society.

"Amitriptyline has been studied for a long time in diabetic neuropathy, so we were not surprised it's used," said lead author Ariel Berger, MPH, of Policy Analysis Inc., Brookline, Mass., in an interview. "What was surprising to us was that nearly half of patients had evidence of potentially inappropriate prescribing. [Physicians] had red alerts, prior to beginning therapy, but they prescribed them anyway."

Mr. Berger and his associates at Pfizer Inc. and Oregon Health and Science University, Portland, identified all patients in a large health-claims database who were diagnosed with diabetic peripheral neuropathy, were aged 65 years or older, and had received a prescription for a tricyclic antidepressant (TCA).

The researchers documented which specific TCAs the patients received, their average daily dose, and the number of medication refills. Finally, they documented specific contraindications, warnings, and precautions listed on the TCA package inserts and compared these with the patients' medical records.

A total of 296 elderly patients received a prescription for a TCA. Nearly half (45.3%) had a diagnosis (cardiovascular disease) or concurrent prescription (thyroid medication) listed among the contraindications, warnings, or precautions in TCA product labeling.

Eight out of 10 who received TCAs received amitriptyline, considered by many to pose the most risk for patients over age 65 years.

Guidelines for the treatment of older patients advise physicians that TCAs in general—and amitriptyline in particular—are potentially dangerous in the elderly. In 1999, the Health Care Financing Administration (now the Centers for Medicare and Medicaid Services) recommended the use of nortriptyline in its place.

The package insert for amitriptyline advises doctors to carefully monitor patients with cardiovascular disorders and notes that the medication can cause cardiac arrhythmias, sinus tachycardia, myocardial infarction, and stroke, as well as both elevated and depressed blood sugar levels.

Pfizer, the study sponsor, has received FDA approval to market the anticonvulsant pregabalin for treatment of diabetic peripheral neuropathy. ■

Peripheral Symptoms Strike Even Well-Controlled Disease

BY DOUG BRUNK
San Diego Bureau

SAN DIEGO — Diabetic peripheral neuropathy was the most common microvascular complication among people with diabetes who underwent a comprehensive annual diabetes assessment, Robyn Anderson reported in a poster session at the annual scientific sessions of the American Diabetes Association.

"We expected to see more retinopathy, but this was a fairly healthy population [of people with diabetes]," said Ms. Anderson, an epidemiologist with the International Diabetes Center, Minneapolis.

"These were people coming in for a 3-hour comprehensive diabetes visit, so we recruited from that pool. They were already very motivated patients, to come in and get help." She also noted that 84% of the patients had type 2 diabetes, "so if there had been a higher prevalence of type 1, it's possible we may have detected more retinopathy."

In a study led by Mary L. Johnson, a registered nurse at the center, Ms. Anderson and her associates evaluated 206 patients for microvascular complications during their annual diabetes visit. Their mean age was 57 years, more than half (54%) were female, and their average hemoglobin A_{1c} level was 7.3%.

The investigators collected data on hemoglobin A_{1c}, lipids, and microalbuminuria, and they also conducted several screenings including the nonmydriatic retinal photo, nerve conduction tests, the Michigan Neuropathy Screening Instrument (MNSI), the vibration detection threshold (VDT), and Neuropathy Total Symptom Score–6.

They defined diabetic peripheral neuropathy as an MNSI score of greater than 2.0 plus either VDT greater than or equal to the 95th percentile or abnormal nerve conduction. Complete data were available for 166 of the 206 patients.

The investigators identified microvascular complications in 48% of patients.

The 10-g microfilament test identified 16% of patients who screened positive for diabetic peripheral neuropathy, yet about twice as many (31%) met the clinical definition of diabetic peripheral neuropathy. At the same time, symptoms of diabetic peripheral neuropathy were observed in 63% of all patients.

Nephropathy was found in 20% of patients and diabetic retinopathy was identified in 11% of patients.

In their poster, the investigators wrote that the observations "support more extensive and systematic screening for diabetic peripheral neuropathy (including both symptoms and clinical exam) in addition to 10-g microfilament exam in diabetes patients with and without known diabetic microvascular complications."

Eli Lilly & Co. sponsored the study. ■

New Drug Shows Promise for Diabetic Nephropathy Patients

BY DOUG BRUNK
San Diego Bureau

SAN DIEGO — Ruboxistaurin, a specific protein kinase C beta inhibitor, had favorable effects on albuminuria and renal function in patients with diabetic nephropathy, according to results from the first human trial of the drug.

"Ruboxistaurin is a promising novel therapy that may improve upon established therapies for diabetic nephropathy," Katherine R. Tuttle, M.D., said at the annual scientific sessions of the American Diabetes Association.

A lot of data show "that diabetic nephropathy, even in advanced stages, is potentially reversible. Perhaps this builds that bit of evidence. Large-scale trials should be performed to confirm its effectiveness and safety."

Developed by Eli Lilly & Co., ruboxistaurin is the first of the specific protein kinase C beta inhibitors being investigated for the treatment of diabetic peripheral neuropathy, diabetic retinopathy, and diabetic nephropathy.

In a year-long multicenter, randomized, double-blind trial funded by Lilly, Dr. Tuttle and her associates randomized 123 subjects to receive ruboxistaurin 32 mg/day or placebo. Study participants who were taking ACE inhibitors, angiotensin receptor blockers, or both remained on the drugs for the entire trial.

Over the course of 12 months, investigators at 17 sites in the United States obtained periodic measurements of the participants' urinary albumin/creatinine ratio (ACR), blood pressure, estimated glomerular filtration rate (GFR), and hemoglobin A_{1c} levels.

By month 12, the mean ACR had decreased by 24% among subjects in the ruboxistaurin group but had not changed in the placebo group, reported Dr. Tuttle of Providence Medical Research Center and The Heart Institute of Spokane, Washington.

The change in urinary ACR in the ruboxistaurin group appeared as early as 1 month into the study and was maintained over the 12-month trial. The mean estimated GFR declined by a mean of 4.8 mL/min per year in the placebo group but did not change significantly in the ruboxistaurin group.

Blood pressure and hemoglobin A_{1c} levels did not differ significantly between the two groups over the study period.

The most frequently reported adverse event was hypertension, which required intervention in 8% of subjects in the placebo group, compared with none in the ruboxistaurin group.

Dr. Tuttle, who is a paid consultant to Lilly, noted that it will take "at least several hundred if not more" subjects per treatment arm to confirm the findings in a future trial.

Diabetic nephropathy develops in about 40% of people with type 2 diabetes and is responsible for 40%-50% of incident end-stage renal disease in the United States. ■

Becaplermin Improves Healing of Diabetic Neuropathic Foot Ulcers

BY HEIDI SPLETE
Senior Writer

CHICAGO — Diabetic neuropathic foot ulcers treated with becaplermin were 30% more likely to heal during a 20-week study than ulcers not treated with the drug, David J. Margolis, M.D., said at the annual meeting of the Wound Healing Society.

The need for effective treatment is great, Dr. Margolis noted. Approximately 12% of diabetic patients develop foot ulcers; 80,000 amputations per year are attributed to diabetes.

In a retrospective cohort study of 25,098 patients, 10% were treated with becaplermin (Regranex), a topical recombinant human platelet-derived growth factor (rhPDGF).

The relative risk that the becaplermin-treated ulcers would heal after 20 weeks was 1.33 compared with standard care, and the relative risk of amputation was 0.86, similar to results from previous clinical trials, said Dr. Margolis, of the University of Pennsylvania. He and his colleagues estimated treatment effectiveness, rather than efficacy, by using propensity scores to control for selection bias.

Propensity studies involve additional probability and attempt to pin down which demographic factors contribute to results in a real-world setting. "We are trying to model why people received therapy," Dr. Margolis said. The cases were drawn from a database of patients treated between 1998 and 2004 at a wound care center affiliated with Curative Health Services. "Some people had only 2 weeks of treatment, and others had 20 weeks," Dr. Margolis noted. The mean length of treatment was 14 weeks.

Overall, 13% of the patients were treated with rhPDGF, and in general, these patients were more likely to be younger and male, and to have older wounds, than patients who were not treated with rhPDGF, he noted.

When asked how the Food and Drug Administration regards propensity studies, Dr. Margolis admitted that data of this type are not likely to prompt a change in drug labeling, for example. However, the FDA recognizes that the large sample size used in propensity score studies can provide useful information, he added.

The study was supported in part by funding from Ethicon Inc., which produces becaplermin (Regranex). ■