Drug Monitor

Dual-function Relief in Diabetic Peripheral Neuropathy

It's common for patients with diabetic peripheral neuropathy to also have cardiovascular autonomic neuropathy (CAN). The usual interventions for CAN target the reduced heart rate variability (HRV) associated with the condition but may do nothing to help the autonomic dysfunction. Gabapentin, however, may work on both fronts.

Researchers from Baskent University Medical School in Ankara, Turkey, gave 30 consecutive patients with type 2 diabetes mellitus and peripheral neuropathy therapeutic doses of gabapentin, titrated as needed for neuropathic symptoms up to a daily dose of 2,400 mg for 3 months. These patients were matched with 28 consecutive control participants who had no evidence of cardiovascular disease.

The researchers found that treatment patients' mean (SD) standard deviation of all NN intervals (SDNN), used to reflect diminished vagal and increased sympathetic modulation of sinus mode, was 106.2 (29.8) ms at baseline and 119.4 (25) ms at 3 months (P = .016). This group's high frequency (HF) values, used as a marker of the parasympathetic nervous system and sympathetic and parasympathetic activity, also improved from baseline to 3 months (mean [SD] HF = 133.6 [98.3] ms^2 vs 167.6 [118.3] ms^2; P = .021). Although their low frequency (LF) values remained similar at baseline and 3 months (mean [SD] LF = 341.8 ms^2 [247.8] vs 352.3 ms^2 [228.9]; P = .88), their LF/HF ratio, which reflected sympathovagal balance, decreased significantly (mean [SD] 3.3 [2.4] ms^2 vs 2.3 [1.9] ms^2; P = .039).

Although the improved HRV values of treatment patients still were low compared with those in the control group, gabapentin did alleviate neuropathic symptoms and improved cardiac autonomic functions in the patients with diabetes. Most (83%) of the patients tolerated gabapentin well; the dose was easily titrated up to 2,400 mg/day. Five patients had dose-related, mild-to-moderate somnolence or dizziness requiring dose adjustment.

Gabapentin was originally designed to mimic the effects of the neurotransmitter GABA. This is the first study to test possible effects of gabapentin on the cardiac autonomic functions. Although they observed a beneficial effect of gabapentin on HRV parameters in their study, the researchers say they don't know the exact mechanism of the drug's action. With recognition of this added effect on cardiac autonomic functions, patients with diabetes and no peripheral neuropathy also may benefit from gabapentin use.

Source: *J Diabetes Complications.* 2010;24(4):229–233. doi:10.1016/j.jdiacomp.2008.12.001

When IBD Treatment Doesn't Work: A New Option

Inflammatory bowel diseases (IBDs) such as ulcerative colitis and Crohn disease are characterized by high levels of granulocytes, lymphocytes, plasma cells, and macrophages, which produce cytokines that further stimulate the local inflammation. Targeting the cells that collaborate to make the condition worse makes sense, so researchers from South Hospital in Stockholm, Sweden, investigated whether the known anti-inflammatory effects of granulocyte/monocyte adsorption (GMA) would help patients with IBDs who haven't responded to standard treatment.

The open-label, observational study involved 15 patients consecutively admitted to South Hospital with ulcerative colitis and 25 with Crohn disease. Both groups of patients had chronic active inflammation that was refractory to treatment with corticosteroids, 5-aminosalicylates, azathioprine, or 6-mercaptopurine. The patients received weekly GMA sessions for 5 to 10 weeks, with up to 3 additional sessions if needed.

The GMA apheresis procedure lasted 1 hour and involved an extracorporeal circuit interposed between 2 veins. The apheresis column contains cellulose acetate beads and, as blood circulates, granulocytes and monocytes are adsorbed to the beads while lymphocytes and erythrocytes pass through to the patient through the column outflow line. The adsorbed cells are replaced with inactivated leukocytes from bone marrow.

Of the 40 patients, 34 (85%) responded to GMA treatment. Further, 26 patients achieved clinical as well as endoscopic remission for an average of 14 months—in 1 case, 58 months. All 26 responders remained steroid-free during the follow-up period, suggesting substantial steroid-sparing effects for GMA.

Close to 100% of patients who initially responded to a course of GMA also responded to subsequent GMA retreatment, which may serve as a guide to selecting responders, the researchers say. For instance, during the follow-up time, 14 of 26 patients who initially achieved symptom remission relapsed. They were

retreated with GMA; 13 achieved a second remission. Following further relapses, 7 patients were successfully retreated for a third time, 3 patients for a fourth time, and 1 patient for a fifth time. Two patients, however, deteriorated in the second and fourth retreatment. One went into remission after additional intravenous corticosteroid treatment; the other after infliximab treatment.

Source: *BMC Gastroenterology.* 2010;10:73. http://www.biomedcentral.com/1471-230x/10/73

Agranulocytosis and Liver Toxicity With Ticlopidine

Although ticlopidine has been associated with some serious adverse effects, most are mild and transitory. Clinicians from San Paolo Hospital in Milan, Italy, report the case of a patient who developed agranulocytosis and hepatic toxicity when given ticlopidine after a vertebrobasilar stroke.

The 70-year-old woman was admitted to the rehabilitation ward of the facility because of gait ataxia after her stroke, which had occurred 10 days before. The patient had no history of hematologic or liver disease, alcohol abuse, or blood transfusion. She was taking aspirin, atorvastatin, and amlodipine. Immediately after her stroke, she stopped taking aspirin and started ticlopidine 250 mg twice per day.

Upon admission, her blood test results were normal. About 4 weeks later she developed agranulocytosis. Liver function tests revealed a mixed cholestasis and hepatocellular injury. She had no fever and no symptoms. Total and direct bilirubin and coagulation tests were normal.

An abdominal ultrasound scan revealed liver steatosis but did not highlight any alterations in the intrahepatic and extrahepatic biliary pathways and, in particular, showed no sign of dilation.

Her physicians immediately stopped ticlopidine therapy and started her on aspirin and dipyridamole. She was also given granulocyte colony stimulating factor. On the second day of aspirin and dipyridamole treatment, her white blood cell count was normal, and her liver function tests progressively improved, returning to normal after 4 weeks.

The authors note that the pathogenesis of ticlopidine's toxic effects is unclear. There is no test that can confirm the diagnostic hypothesis of the drug toxicity apart from excluding other possible causes and the normalization of blood tests after the drug is stopped, which is what happened with their patient.

The latent period between starting ticlopidine and the appearance of liver toxicity ranges from 1 week to 6 months, but in most patients it appears within 2 to 12 weeks. Hepatic toxicity is not dose dependent and not related to treatment duration, the authors say. When the drug is discontinued, symptoms and liver abnormalities usually resolve within 3 months.

Hepatic toxicity induced by ticlopidine is underestimated, the authors warn. Because those first 3 months are critical in determining toxic effect presence, they strongly urge regular checks of liver function.

Source: *J Med Case Reports.* 2010;4:269. http://www.jmedicalcasereports.com/content/4/1/269

Probiotics vs Antibiotics for Bacterial Vaginosis

Although the cause of bacterial vaginosis (BV) hasn't been fully elucidated, most studies say recurrent BV is due to relapse, not reinfection. Further, abnormalities of the vaginal flora often persist even in the absence of clinical symptoms. Using probiotics, say researchers from Yuyao/Xinhua Hospital in Shanghai, China, "dramatically" reduced recurrence by balancing the flora.

In a double-blind, placebo-controlled study, the researchers assessed the effectiveness of vaginal probiotic capsules to prevent BV relapse in 120 healthy women with a history of recurrent BV. The women used 1 probiotic capsule daily for 7 days on, 7 days off, and 7 days on.

Over 11 months of follow-up, 9 of 57 women (16%) using probiotic prophylaxis had recurrent episodes of BV, compared with 27 of 60 women (45%) taking placebo. Probiotics also lowered rates of *Gardnerella vaginalis* through 2 months (2 women in the probiotic group vs 11 in the placebo group developed this infection).

This trial represents the first report of vaginal probiotic capsules used solely to prevent BV recurrence. The researchers say the capsules compare favorably with daily yogurt consumption (studies have found poor adherence) and metronidazole. They note, in fact, that authors of a recent Cochrane Review reported that treatment with vaginal *Lactobacillus* tablets was more effective than metronidazole for BV. While metronidazole and the probiotic capsules have similar recurrence rates, the drug's adverse effects are concerning. By comparison, probiotic capsules are well tolerated. In addition, probiotic prophylaxis reduced discharge, lowered vaginal pH, and reduced clue cells, although it had little effect on malodor. Subject-reported incidence of vaginal discharge and malodor between 2 and 11 months after treatment were 3 times higher in the control group.

Source: *Am J Obstet Gynecol.* 2010;203(2):120e1–6. doi:10.1016/j.ajog.2010.05.023.