Morphine, Gabapentin work better together than alone for Neuropathic Pain

Combined treatment with morphine and gabapentin is more effective at lower doses than either agent alone at controlling neuropathic pain, according to a report in The New England Journal of Medicine.

Current drugs used to treat neuropathic pain are not entirely effective and have dose-limiting side effects, noted Gilron, from Queen’s University in Kingston, Ontario, Canada. Thus, there is a need for novel drug combinations to combat this problem.

In a crossover trial, 57 patients with painful diabetic neuropathy or post-herpetic neuralgia were randomised to receive active placebo (lorazepam), sustained release morphine, gabapentin, or morphine plus gabapentin for 5 weeks. A total of 41 patients completed the trial.

At baseline, the subjects had an average daily pain score of 5.72 on a 0-10 scale. With morphine plus gabapentin at the maximal tolerated dose, the score improved to 3.06, whereas with the other treatments the score never fell below 3.70 (p < 0.05). Similar findings were obtained when the Short-Form McGill Pain Questionnaire was used for assessment.

When given in combination, the maximal tolerated doses for morphine and gabapentin were significantly lower than when the agents were used alone, the investigators point out. At maximal tolerated doses, morphine plus gabapentin was more likely than gabapentin monotherapy to be linked to constipation and more likely than morphine monotherapy to be tied to dry mouth (p < 0.05 for both).

In a related editorial, Srinivasa N. Raja and Jennifer A. Haythornthwaite, from Johns Hopkins University in Baltimore, comment that “this study clearly shows the advantages of concurrent titration of gabapentin and morphine, though the perceived risks of addiction and diversion with opioids and the fear of scrutiny by regulatory agencies may present barriers to the acceptance of this combination as first-line treatment.”


Diabetes-related Hypoglycaemia Risk Greater with Jogging than with Team Sports

For active diabetics, moderate-intensity exercise such as light continuous jogging or cycling poses a greater risk of hypoglycaemia than intermittent high-intensity exercise representative of the activity patterns of team and field sports such as soccer or hockey.

“Our finding has implications for safe participation in exercise by individuals with type 1 diabetes,” said Kym Guelfi, who led the study. The observation is important, since many individuals with type 1 DM are discouraged from engaging in vigorous exercise because of a fear of exercise-induced hypoglycemia.”

The researchers analyzed the response of blood glucose and gluco-regulatory hormones on two separate occasions during which seven healthy young patients...
with type 1 diabetes performed either a 30-minute moderate-intensity (MOD) or intermittent high-intensity exercise (IHE) protocol.

MOD consisted of continuous exercise at 40% peak oxygen consumption (VO2) while IHE entailed a combination of continuous exercise at 40% peak VO2 interspersed with sprints performed every 2 minutes to simulate the activity patterns of team sports.

The experiment was designed to reproduce a "real-life" situation in which insulin is injected and food is consumed as per normal before exercise, the team explains.

They found that both MOD and IHE exercise protocols led to a decline in blood glucose levels, but the decline was greater with MOD than with IHE - 4.4 vs. -2.9 mmol/L; p < 0.05) -- despite a higher heart rate and greater total work load with IHE.

During the 60-minute recovery period after exercise, glucose levels remained higher in IHE compared with MOD (p < 0.05). Blood glucose levels remained stable during recovery from IHE whereas they continued to decline after MOD.

The attenuated fall in blood glucose with IHE is most likely due to the observed increase in catecholamine and growth hormone levels stimulated by the intense exercise.

"Hopefully this study will contribute to improved guidelines for individuals with type 1 diabetes to manage their glucose levels during and after exercise to avoid hypoglycaemia. However, caution should be taken in generalising these findings until further research has been conducted." Guelfi said.

Source: Diabetes Care 2005;28:1289-1294

Both overall obesity, denoted by higher body mass index (BMI), and abdominal obesity, reflected by higher waist circumference, strongly and independently predict risk of type 2 diabetes in men, but abdominal obesity appears to be the better predictor.

"Both BMI and waist circumference are useful for assessing health risk and should be measured in clinical settings and epidemiological research whenever possible," the investigators say. "But abdominal fat measured by waist circumference can indicate a strong risk for diabetes whether or not a man is considered overweight or obese according to his BMI," lead author Youfa Wang added.

In the study, investigators compared the predictive power of BMI, waist circumference (WC) and waist-to-hip ratio (WHR) for the development of type 2 diabetes in 27,270 men participating in the Health Professionals Follow-up Study.

During 13 years of follow up, a total of 884 men developed type 2 diabetes, Wang and colleagues from Johns Hopkins Bloomberg School of Public Health in Baltimore, report in the March issue of the American Journal of Clinical Nutrition.

According to the team, the age-adjusted relative risks across quintiles of WC, starting at a WC of 73.7 to 86.4 cm and going up to 101.6 to 157.5 cm, were 1.0, 3.0, 3.6, 5.0, and 12.0, respectively.

For WHR, relative risks across increasing quintiles were 1.0, 1.1, 1.8, 2.9, and 6.9 and for BMI they were 1.0, 1.1, 1.8, 2.9, and 7.9, respectively.

These findings support the contention that the measurement of WC should be used in clinical practice instead of WHR, suggest the investigators.

The study findings also suggest that the currently recommended cut-off for high waist circumference of 102 cm for men may need to be lowered to 95 cm. Many of the men who developed type 2 diabetes had measurements lower than the cut-off, and the risk associated with the waist circumference increased at a much lower level.

Source: Am J Clin Nutr 2005;81:555-563

(See article on page 3 re: modified guidelines)
The American Heart Association (AHA) and the National Heart, Lung, and Blood Institute (NHLBI) have jointly issued new guidance for the diagnosis and management of the metabolic syndrome (MS) in adults. Their statement confirms the recommendations of the National Cholesterol Education Program Adult Treatment Panel III (ATP III). Some people with obesity have accumulated risk factors as a result of that, and deserve special attention. ATP III suggests that MS can be diagnosed when 3 of 5 criteria are present: elevated waist circumference, triglycerides, blood pressure (BP), fasting glucose (FG), and reduced HDL cholesterol.

While measured under normal conditions, insulin sensitivity was reduced by 50% in the obese subjects. This was also true of mean 24-hour insulin clearance due to a 50% reduction in hepatic insulin extraction. Over 24 hours, insulin secretion was doubled in the obese patients. Despite this hypersecretion, beta-cell glucose sensitivity, rate sensitivity and potentiation were similar to those in controls.

Ten of the morbidly obese patients underwent bilio-pancreatic diversion consisting of a partial gastrectomy with distal Roux-en-Y reconstruction. As Ferrannini noted, “surgical diversion of bile flux into the lower intestine induces massive weight loss.”

It also resulted in a surprising recovery of insulin action in a follow-up of eight of the surgery patients. At 6 months, when they had lost a mean of 33 kg, both insulin hypersecretion and insulin sensitivity were normalised.

At 2 years, when weight loss had reached 50 kg, insulin sensitivity was supernormal. Insulin secretion over 24 hours, which had been 468 nmol prior to surgery, compared to 235 nmol in controls, fell to a lower-than-normal 167 nmol.

Thus, the researchers conclude that "malabsorptive bariatric surgery corrects both the insulin hypersecretion and the insulin resistance at a time when BMI is still high."

Source : Diabetes 2005;54:2382-2389

"Increased fasting glucose levels have been adjusted from 6.1 to 5.6 mmol/l."

"Severely obese patients have to secrete large amounts of insulin to compensate for their resistance to insulin action. Their beta-cell function, however, is fine as long as their glucose tolerance is not impaired."
Nerve Auto-antibodies tied to Peripheral Autonomic Neuropathy in Diabetics

Auto-antibodies directed against autonomic nerves are associated with the subsequent development of cardiac and peripheral autonomic neuropathy in diabetic patients, European researchers report. In fact, Viktoria Granberg said, "Our study showed that patients with autonomic nerve auto-antibodies had a seven-fold increased risk of developing autonomic neuropathy."

Granberg from Malmo University Hospital, Sweden and colleagues note in Diabetes Care that although certain studies have suggested that there may be some correlation between autonomic nerve auto-antibodies (ANabs) and autonomic dysfunction, "this has been difficult to establish."

To investigate further, the researchers prospectively followed 41 patients with type 1 diabetes. After a baseline examination covering autonomic nerve function, they were examined three more times over the course of 13 to 14 years. At the third examination, at about 6 years, blood samples were taken for ANabs analysis.

A total of 23 patients (56%) showed evidence of ANabs. Among this group, the frequency of at least one abnormal cardiac autonomic nerve function test at the third examination (74%) and fourth examination (71%) was significantly higher than in the ANabs-negative patients (39% and 25%). No such differences had been seen at the first and second examinations.

Over the follow-up period, ANabs-positive patients showed a relative risk of developing cardiac neuropathy some 7.5 times that of the other patients. Moreover, further testing showed associations between ANabs and both sympathetic and parasympathetic autonomic dysfunction.

The researchers thus conclude that "autonomic neuropathy in type 1 diabetes may have an autoimmune background."

Source: Diabetes Care 2005;28:1959-1964

Oral Insulin does not Delay Type 1 Diabetes in those at Risk

Oral insulin does not appear to delay or prevent type 1 diabetes in those at risk for the disease, according to findings published in the May issue of Diabetes Care.

Jay S. Skyler, from the University of Miami, Florida, and colleagues with the Diabetes Prevention Trial-Type 1 Study Group examined whether administration of oral insulin could delay or prevent type 1 diabetes in non-diabetic relatives of those with the disease.

In a double-blind, placebo-controlled trial, 2523 islet cell antibody-positive patients underwent staging to quantify the risk of developing diabetes. Of these, 372 were classified as having an intermediate risk and were randomised to oral insulin (7.5 mg/d) or placebo.

Oral glucose tolerance tests were performed every 6 months to assess glycaemic status. The subjects were followed for a median of 4.3 years. The primary end point was diabetes diagnosis.

Diabetes was diagnosed in 44 patients receiving oral insulin and 53 patients receiving placebo. The annualised rate of diabetes was similar in the oral insulin and placebo groups, at 6.4% and 8.2%, respectively. No difference was observed between the groups in glycaemia in the intention-to-treat analysis.

"There were no serious adverse events and no differences between groups in frequency of adverse events," Skyler's team writes. No episodes of severe hypoglycaemia were reported.

A "suggestion of benefit" of oral insulin was seen in a subgroup of patients with insulin auto-antibodies who had an annualised diabetes rate of 6.2% with oral insulin compared with 10.4% with placebo. "Further studies are needed to explore the potential role of oral insulin in delaying diabetes in relatives similar to those in the subgroup with higher insulin auto-antibody levels," the investigators conclude.

Source: Diabetes Care 2005;28:1068-1076