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## Exenatide (Exendin-4)-Induced Pancreatitis

### A case report

Exenatide is a 39-amino acid peptide approved for the adjunctive treatment of type 2 diabetes. It is an incretin mimetic agent that is consistent in activity with the actions of glucagon-like peptide 1. Proposed mechanisms of action include enhanced glucose-dependent insulin secretion from pancreatic  $\beta$ -cells, restoration of first-phase insulin response, suppression of glucagon secretion, and delay of gastric emptying. Kendall et al. (1) found no evidence of cardiovascular, pulmonary, hepatic, or renal toxicities with exenatide. Nausea (39–48%) and hypoglycemia (19–27%) were the most common side effects reported.

A 69-year-old man with type 2 diabetes of 15 years' duration presented for follow-up. He had known diabetic neuropathy and retinopathy. His medical history was remarkable for coronary artery disease, gastroesophageal reflux dis-

ease, rheumatoid arthritis, and colonic polyposis. He was taking metformin at 500 mg p.o., a.c., b.i.d.; pioglitazone at 30 mg p.o. daily; NPH insulin at 45 units s.q., a.c., in the morning, and 20 units s.q., a.c., in the evening; insulin aspart on a sliding scale; metoprolol at 50 mg p.o. daily; gabapentin at 1,200 mg p.o. daily; lovastatin at 40 mg p.o. daily; irbesartan at 150 mg p.o. at bedtime; clopidogrel at 75 mg p.o. daily; infliximab at 3 mg/kg i.v. every 8 weeks; ezetimibe 10 mg p.o. daily; and esomeprazole at 40 mg p.o. daily. Remarkable findings on examination were exogenous obesity, bilateral retinal dot hemorrhages, trace pitting bipedal edema, hyperpigmentation of the legs, and a symmetric distal stocking polyneuropathy. The patient was 6 ft tall and weighed 268 lb. HbA<sub>1c</sub> level was 10.5%.

Treatment options were discussed, and exenatide at 5 mg s.q. b.i.d. was initiated. The pioglitazone and the metformin were discontinued. Within 24 h of initiating the exenatide, the patient developed a midepigastic abdominal pain that radiated through to the back. As he continued with the exenatide therapy the pain intensified. There was no fever or chills. He denied alcohol use or exposure to new medication. There was no previous history of pancreatitis or gallstones.

The patient presented to the emergency room on the 5th day of therapy. He was noted to have a glucose level of 309 mg/dl, creatinine of 1.0 mg/dl, and CO<sub>2</sub> of 27, and ketones were negative. Aspartate aminotransferase was 25 IU/l and alanine aminotransferase 25 IU/l. Serum triglycerides were 150 mg/dl, serum calcium was 8.6 mg/dl, white blood cell count was 11,000, and hemoglobin was 13.8 g/l. Serum amylase was 384 IU/l and serum lipase 346 IU/l. Computed axial tomography scan of the abdomen revealed no evidence of cholelithiasis. The presumptive diagnosis of acute pancreatitis was made. Intravenous fluids along with intravenous pantoprazole were started. He was made NPO (nothing to eat), and a gastroenterologic consultation was obtained. The NPH and the exenatide were withheld. A weight-based sliding scale of insulin was started using aspart.

On subsequent days the lipase was 106, 27, and 17 IU/l. The abdominal pain resolved by day 3. Clear fluids were started, and the diet was advanced without difficulty. The patient was discharged home without sequelae.

We report a case of acute pancreatitis

in which exenatide appears to be the etiologic agent. A review of the literature failed to reveal any previously reported cases of exenatide-induced acute pancreatitis. An occult etiology for the pancreatitis cannot be completely discounted. Pancreatitis has been reported with mevacor, infliximab, and gabapentin, but their protracted use without change in dose mitigates their being the etiologic agent. The temporal relation of the symptoms to the onset and cessation of therapy along with the normalization of laboratory parameters on drug withdrawal implicates exenatide as the cause. Caution should be exercised when prescribing exenatide with agents known to cause pancreatitis and in patients at high risk.

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## The Use of Insulin Glargine With Gestational Diabetes Mellitus

We agree with the recent letter by Woolderink et al. (1) that insulin glargine use during pregnancy may be appropriate. In contrast to that letter, which described the use of insulin glargine in pregnant women with type 1 diabetes, we detail the use of insulin glargine in four patients with gestational diabetes mellitus (GDM). Target blood glucose levels set by the American College of Obstetricians and Gynecologists for women with GDM include fasting glucose  $\leq 95$  mg/dl and 1-h postprandial glucose  $\leq 130$ –140 mg/dl or 2-h postprandial glucose  $\leq 120$  mg/dl (2). These criteria are used by the Maternal-Fetal Medicine

Clinic at Wake Forest University School of Medicine to determine the need for insulin.

The four women whose treatment we describe here were referred to our clinic and delivered between 1 December 2003 and 31 March 2005. The decision to initiate insulin glargine in these patients was based on postprandial self-monitored blood glucose readings <150 mg/dl. All four maintained blood glucose values that, on average, met the American College of Obstetricians and Gynecologists' criteria for the remainder of their pregnancies using insulin glargine alone. Two of four patients had average fasting blood glucose values  $\leq$ 95 mg/dl; the other two maintained average fasting blood glucose values  $\leq$ 98 mg/dl. Their starting doses of insulin glargine ranged from 10 to 50 units, with an average of 29 units. Doses at delivery ranged from 18 to 78 units, with an average of 44 units.

For three patients with well-documented blood glucose values before initiating insulin glargine, the average reduction in fasting blood glucose was 15 mg/dl and the average postprandial decrease was 17 mg/dl. One patient experienced an average blood glucose reduction of 30 mg/dl, including reductions from 21 mg/dl after breakfast to 49 mg/dl after dinner.

All four women reported successful pregnancy outcomes. No infants were reported to have hypoglycemia, and one weighed >9 lb. One patient experienced hypoglycemic episodes using insulin glargine, with six episodes of blood glucose <60 mg/dl (53, 57, 54, 54, 59, and 58 mg/dl). She also reported skipping meals, especially breakfast. All six of her hypoglycemic episodes were in the time period labeled "2 h after breakfast."

Starting doses of insulin glargine were implemented using half of the estimated total daily dose needed during that trimester. Total daily dose was calculated as 0.4–0.5 units/kg in the 1st trimester, 0.5–0.6 units/kg in the 2nd trimester, or 0.7–0.8 units/kg in the 3rd trimester. Insulin glargine was injected in the morning before breakfast and increased rapidly until blood glucose was at target. Throughout the rest of the pregnancy, insulin glargine doses were advanced by 3–5 units whenever readings reached the upper limit of the target range.

Morning dosing of insulin glargine contributed to target postprandial readings throughout the day, with no nocturnal hypoglycemia reported and without

altering fasting glucose levels. Though the usual recommended starting dose of insulin glargine is 10 units, we found that higher starting doses were required to achieve blood glucose goals during pregnancy, especially in obese women.

Multiple studies (3–5) over many years have shown that tight glucose control during pregnancy is important to promote normal perinatal outcomes. Insulin glargine offers an alternative in GDM, especially for women with mild glucose intolerance. Additional research is needed to further elucidate the safety and effectiveness of using insulin glargine in women with GDM.

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## Bowel Dysfunction in Wolfram Syndrome

**B**owel dysfunction is a common problem in patients with metabolic/neurological disorders and ranges from constipation and intestinal pseudo-obstruction to intractable fecal incontinence. However, the mechanism of it remains not entirely clear, although the bowel dysfunction severely affects the quality of life in the patients.

Here, we report on a 32-year-old man with clinically diagnosed Wolfram syndrome (WFS), which is thought to be caused by a *WFS1* gene mutation that encodes *wolframin*, an endoplasmic reticulum calcium channel in neurons and pancreatic  $\beta$ -cells. He also presented with severe bowel (urgent fecal incontinence that started at age 24 years) and bladder dysfunction. His previous illnesses included congenital cataracts, progressive optic atrophy that started at age 3 years, and diabetes that started at age 11 years (under insulin treatment). At that time, he had first begun to have mild urinary urgency/frequency. At age 21 years, he was found to have hearing loss and diabetes insipidus (then, urine output 1,200 ml/day under desmopressin treatment with no upper urinary tract dilatation). A nerve conduction study in the extremities revealed sensory-dominant axonal neuropathy. A brain magnetic resonance imaging scan revealed atrophy in the cerebellum and the brainstem, although he had no cerebellar ataxia. Urodynamic study with pressure-flow analysis showed detrusor filling overactivity/voiding underactivity without detrusor-sphincter dyssynergia. Twenty milligrams a day of propiverine, an anticholinergic agent, once ameliorated his bladder and bowel symptoms. However, he again became fecally incontinent, and after tapering the drug, we performed a bowel function test in the patient. Colonic transit time test using Sitzmarks (1) showed normal colonic transit time (24.0 h, 16.0 < normal < 48.0). However, videomanometry (1) showed loss of spontaneous phasic rectal contractions (SPRCs) that were seen in normal subjects and sphincter weakness. Then he was taught to perform pelvic floor exercise, and his fecal incontinence became slightly ameliorated.

Bladder dysfunctions reported in WFS include hydroureter due to excessive urine output (2), detrusor-sphincter dyssynergia (2), and detrusor overactivity