**Journal of Diabetes Science and Technology**
Volume 4, Issue 1, January 2010


COMMENTARY

# Do Incretin-Based Therapies Cause Acute Pancreatitis?

Leann Olansky, M.D.

## Abstract

In 2007 a question was raised about the causal relationship between the first of the glucagon-like peptide 1 receptor agonists, exenatide, and pancreatitis, as postmarketing reports of pancreatitis in patients treated with this agent had been received by the Food and Drug Administration (FDA). There had been six reports of hemorrhagic pancreatitis, with two of the cases resulting in death. An update of the package insert for Byetta was mandated. Sitagliptin entered the market about a year and a half later, and now there are similar reports of acute pancreatitis. As the number of patients treated with these agents increases, is it uncovering a risk not appreciated in the premarket phase or just what should be expected from the population treated with these agents? To date, 88 cases of acute pancreatitis have been reported to the FDA in patients taking sitagliptin (Januvia/Janumet). Of these, two cases have been hemorrhagic or necrotizing pancreatitis. A revision of the package insert for sitagliptin has been made recently. An examination of available data should help shed light on whether the relation is likely causal or merely incidental.

*J Diabetes Sci Technol 2010;4(1):228-229*

## Drug-Induced Pancreatitis

In a 2005 review, Trivedi and Pitchumoni[1] reported that, of the top 100 prescribed drugs in the United States, 44 have been associated with acute pancreatitis. These include over-the-counter agents such as acetaminophen, common antibiotics such as trimethoprim/sulfamethoxazole and erythromycin, agents used to treat human immunodeficiency virus/acquired immunodeficiency syndrome, and oncologic agents.[1] No clear pathophysiologic basis connects the various agents. In 2002, Blomgren and colleagues[2] suggested that glyburide may be associated with an increased risk for pancreatitis, but also noted an increased risk when the body mass index exceeded 30.

## Pancreatitis in Type 2 Diabetes

A number of comorbidities associated with type 2 diabetes can predispose to pancreatitis, hypertriglyceridemia, and gallbladder disease.[3–5] Diabetic subjects can also be exposed to alcohol or other drugs, which have been reported to be associated with pancreatitis. What is the risk for pancreatitis in people with type 2 diabetes? Is there evidence for an increase when incretin-based therapies are used to control hyperglycemia?

Pancreatitis in the general population appears to be increasing in Western countries with 60–80% attributed

**Author Affiliation:** Department of Endocrinology, Cleveland Clinic Health System, Cleveland, Ohio

**Abbreviations:** (CI) confidence interval, (FDA) Food and Drug Administration, (RR) relative risk

**Keywords:** exenatide, gallbladder disease, incretin, pancreatitis, sitagliptin, type 2 diabetes

**Corresponding Author:** Leann Olansky, M.D., Department of Endocrinology, Cleveland Clinic Health System, 9500 Euclid Avenue, Cleveland, OH; email address olanskl@ccf.org

to alcohol or gallstones but at least 20% has no clear etiology.[3] New etiologies continue to be described as evidenced by the report by Frulloni and colleagues[6] of an autoimmune pancreatitis identified by a novel antibody directed at an epitope homologous to a protein from *Helicobacter pylori*. Type 2 diabetes is associated with obesity and hyperlipidemia, each of which has been considered a putative risk factor for pancreatitis.[3–5]

Noel and colleagues[7] examined the risk for pancreatitis in subjects with type 2 diabetes using data from a large insurance database (29,332,477 covered lives), identifying type 2 diabetes subjects and subjects without diabetes by medical claims and pharmacy claims covering the period of 1/1/99 to 12/31/05 who were eligible for coverage by the plan. Similarly, medical claims were used to identify episodes of acute pancreatitis and gallbladder disease.[7] A 2.8-fold increased risk of acute pancreatitis was reported in the diabetic cohort overall with a 5-fold risk in the 18- to 44-year-old population. A 3-fold risk in men was reported compared to 2.6-fold in women.[7] The time period examined was important, as exenatide (Byetta) was approved in June 2005 and had limited market penetration during the first 6 months, which was the last 6 months of the study period. Sitagliptin (Januvia), the first of the dipeptidyl peptidase-4 inhibitors, was not yet on the market. A 1.9-fold risk of biliary disease was reported; similarly, a greater relative risk (RR) was also found in the younger population. Cholelithiasis was felt to be the basis in at least 50% of these cases.[7]

The estimated risk for acute pancreatitis in the population at large is estimated to be 0.33–0.44 events per 1000 adults per year.[3,8] Fifteen to 20% of cases are considered to be severe, with 2–4% resulting in death.[8] A relatively small fraction (1–2%) is felt to be drug induced.[8] In the exenatide development program, there have been six cases of acute pancreatitis observed in about 3489 subject-years of exposure (1.7/1000 subject-years) compared to one case in about 336 subject-years in placebo (3.0/1000 subject-years) and one case in about 497 subject-years (2.0/1000 subject-years) for the insulin comparator (Amylin and Lilly data on file).

Dore and colleagues[9] examined a similar claims database for the period of June 2005 through June 2008 including 27,996 exenatide initiators and 16,276 sitagliptin initiators matched with type 2 diabetic subjects taking nonincretin-based therapies. Over a period of 1 year, 0.13% of exenatide users and 0.12% sitagliptin users suffered acute pancreatitis. The risk of pancreatitis was comparable in each group [RR 1.0; confidence interval (CI) 0.6–1.7)] for exenatide and [RR 1.0; CI 0.5–2.0)] for sitagliptin relative to metformin or glyburide.[9]

## Conclusion

Pancreatitis is increased in subjects with type 2 diabetes, which is the clinical population treated with exenatide or sitagliptin. It is unlikely that either agent is causal in the development of acute pancreatitis. As new agents enter the market, we expect similar rates of pancreatitis to be reported as their usage approaches that of currently used agents.

**Disclosure:**

The author has been a speaker for Amylin and Lilly, USA promoting exenatide (Byetta) and for Merck promoting sitagliptin (Januvia/Janumet).

**References:**

1. Trivedi CD, Pitchumoni CS. Drug-induced pancreatitis: an update. J Clin Gastroenterol. 2005;39(8):709-16.
2. Blomgren KB, Steineck G, Sundstrom A, Wiholm BE. Obesity and treatment of diabetes with glyburide may both be risk factors for acute pancreatitis. Diabetes Care. 2002;25(2):298-302.
3. Forsmark CE, Baillie J; AGA Institute Clinical Practice and Economics Committee; AGA Institute Governing Board. AGA institute technical review on acute pancreatitis. Gastroenterology. 2007;132(5):2022-44.
4. Pagliarulo M, Fornari F, Fraquelli M, Zoli M, Giangregorio F, Grigolon A, Peracchi M, Conte D. Gallstone disease and related risk factors in a large cohort of diabetic patients. Dig Liver Dis. 2004;36(2):130-4.
5. Field AE, Coakley EH, Must A, Spadano JL, Laird N, Dietz WH, Rimm E, Colditz GA. Impact of overweight on the risk of developing common chronic diseases during a 10-year period. Arch Intern Med. 2001;161(13):1581-6.
6. Frulloni L, Lunardi C, Simone R, Dolcino M, Scattolini C, Falconi M, Benini L, Vantini I, Corrocher R, Puccetti A. Identification of a novel antibody associated with autoimmune pancreatitis. N Engl J Med. 2009;361(22):2135-42.
7. Noel RA, Patterson RE, Braun DK, Bloomgren GL. Increased risk for acute pancreatitis and biliary disease observed in patients with type 2 diabetes. Diabetes Care. 2009;32(5):834-38.
8. Whitcomb DC. Clinical practice. Acute pancreatitis. N Engl J Med. 2006;354(20):2142-50.
9. Dore DD, Seeger JD, Arnold Chan K. Use of a claims-based active drug safety surveillance system to assess the risk of acute pancreatitis with exenatide or sitagliptin compared to metformin or glyburide. Curr Med Res Opin. 2009;25(4):1019-27.