ONE MINUTE CONSULT

BRIEF ANSWERS TO SPECIFIC CLINICAL QUESTIONS

Q: Do incretin drugs for type 2 diabetes increase the risk of acute pancreatitis?

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A: Probably not. Although cases of acute pancreatitis have occurred in patients taking these drugs, cases have been reported in patients taking other drugs as well. Furthermore, the incidence of acute pancreatitis is higher in patients with type 2 diabetes (for which incretin-type drugs are indicated) than in the general population, regardless of treatment.

INCRETINS, A NEW CLASS OF DRUGS FOR TYPE 2 DIABETES

Incretins are hormones secreted by the small intestine in response to glucose in food. Glucagon-like peptide 1 (GLP-1) is an endogenous incretin that stimulates insulin secretion, suppresses glucagon secretion, and delays gastric emptying.

Current incretin-based therapies for type 2 diabetes include two types of agents. First are drugs that mimic the action of native GLP-1, such as the injectable GLP-1 analogues exenatide (Byetta) and liraglutide (Victoza). Second are agents that interfere with the metabolism of native GLP-1, mainly by inhibiting the endogenous enzyme dipeptidyl peptidase 4 (DPP-4), thus extending the life of native GLP-1. Two DPP-4 inhibitors pertinent to this discussion are saxagliptin (Onglyza) and sitagliptin (Januvia), both of which are taken orally.

The question has been raised whether incretin-based therapy causes pancreatitis. The package inserts for exenatide and sitagliptin have been updated to reflect this possibility, thus causing concern to practitioners. Is this concern warranted?

MANY DRUGS ARE ASSOCIATED WITH ACUTE PANCREATIS

In a review published in 2005, Trivedi and Pitchumoni[1] reported that, of the top 100 prescribed drugs in the United States, 44 had been associated with acute pancreatitis. These agents included over-the-counter drugs such as acetaminophen (Tylenol), common antibiotics such as trimethoprim-sulfamethoxazole (Bactrim) and erythromycin, and drugs used to treat acquired immunodeficiency syndrome and cancer. No clear pathophysiologic basis connects these agents.

In 2002, Blomgren et al[2] suggested that glyburide (Micronase) use might be a risk factor for acute pancreatitis, and that the risk of pancreatitis is higher if the body mass index is 30 kg/m^2 or more. In 2008, more concern was raised with a report of hemorrhagic or necrotizing pancreatitis in six patients taking exenatide, two of whom died.[3] And more recently, reports of 88 cases of acute pancreatitis (including 2 cases of hemorrhagic or necrotizing pancreatitis) from October 2006 to February 2009 in patients taking sitagliptin or the sitagliptin-metformin combination Janumet[4] prompted a revision of the package inserts.

Do these cases represent unexpected toxicities not appreciated in premarket clinical trials, or are they to be expected in the population treated with these agents as greater numbers are exposed?

The risk of acute pancreatitis is higher in type 2 diabetes, regardless of treatment

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TYPE 2 DIABETES ALSO POSES A RISK OF PANCREATITIS

A number of comorbidities associated with type 2 diabetes predispose to pancreatitis, particularly hypertriglyceridemia and gallbladder disease.[5–7] People with diabetes can also be exposed to alcohol or other drugs reported to be associated with pancreatitis.

What is the risk of pancreatitis in patients with type 2 diabetes? Is there evidence of a greater risk when incretin-based drugs are used to control hyperglycemia rather than other agents?

Pancreatitis appears to be increasingly prevalent in the general population in western countries. Some 60% to 80% of cases are attributed to alcohol or gallstones, but 20% do not have a clear cause.

In 2009, a new cause of acute pancreatitis was introduced when Frulloni et al[8] reported that a novel antibody that recognizes epitopes shared with *Helicobacter pylori* was associated with autoimmune pancreatitis. *H pylori* is a common gastrointestinal organism, found in diabetic and nondiabetic patients, and it may well account for what has up to now been considered idiopathic pancreatitis.

Type 2 diabetes is associated with obesity and hyperlipidemia, each of which has been considered a putative risk factor for pancreatits.[5–7]

Noel et al[9] examined the risk of pancreatitis in patients with type 2 diabetes in a large insurance database (29,332,477 covered lives). They identified people with type 2 diabetes and those without diabetes eligible for coverage by the plan, using medical and pharmacy claims from January 1, 1999, to December 31, 2005. The authors also used medical claims to identify episodes of acute pancreatitis and gallbladder disease. They found that the risk of acute pancreatitis was 2.8 times higher in the overall diabetic cohort than in the nondiabetic cohort, and five times higher in the youngest diabetic cohort (ages 18 to 44) than in nondiabetic people of the same age. The risk was three times higher in diabetic men than in nondiabetic men, and 2.6 times higher in diabetic women than in nondiabetic women.

The time period examined in this study is fortuitous, since exenatide was approved in June 2005 and had very little market penetration during its first 6 months, corresponding to the last 6 months of the study period. Sitagliptin, the first DPP-4 inhibitor, had not yet reached the market.

Noel et al[9] also found that the risk of biliary disease in patients with diabetes was 1.9 times higher than in those without diabetes. The relative risk of gallbladder disease was proportionally greater in a younger population with diabetes than in the population without diabetes, in whom the risk of gallbladder disease increases with age. Cholelithiasis was believed to be the underlying cause in at least 50% of the cases of pancreatitis.

Several new drugs for diabetes work via the incretin system

PANCREATITIS AND INCRETIN-BASED THERAPIES

The estimated risk of acute pancreatitis in the population at large is reported as 0.33 to 0.44 events per 1,000 adults per year[10]; 15% to 20% of cases are considered severe, and 2% to 4% result in death.[5,10] A relatively small number (1%–2%) are believed to be drug-induced.[10]

Exenatide. In the exenatide development program, six cases of acute pancreatitis were observed in about 3,489 subject-years of exposure (1.7 per 1,000 subject-years), compared with one case in about 336 subject-years with placebo (3.0 per 1,000 subject-years) and one case in about 497 subject-years (2.0 per 1,000 subject-years) with insulin.[11]

Sitagliptin. Dore et al[12] examined claims from another database for the period of June 2005 through June 2008 to look specifically at the risk with incretin-based therapies. This database included 27,996 people starting exenatide and 16,276 people starting sitagliptin, matched with people with type 2 diabetes taking metformin (Glucophage) or glyburide. Over a period of 1 year, 0.13% of exenatide users and 0.12% of sitagliptin users suffered acute pancreatitis. The risk of pancreatitis was comparable in each group:

- For exenatide, relative risk (RR) 1.0, 95% confidence interval (CI) 0.6 to 1.7, compared with metformin or glyburide
- For sitagliptin, RR 1.0, 95% CI 0.5 to 2.0.

Saxagliptin. In clinical trials of saxagliptin, the incidence of pancreatitis was 0.2% in 3,422 patients receiving saxagliptin and

0.2% in 1,066 controls,[13] similar to the rates for sitagliptin and exenatide.

Liraglutide appeared to be associated with a risk of acute pancreatitis, with seven cases in 3,900 patients receiving liraglutide vs one case in a patient taking another diabetes drug.[14] This rate is similar to that reported in exenatide clinical trials, suggesting that pancreatitis has been underreported in the comparator subjects. We need more experience to see if this agent really poses more risk than other antidiabetic therapies.

As new antidiabetic agents enter the market and their use becomes common, it would not be surprising to see rates of pancreatitis similar to those reported by Blomgren et al[2] in 2002, when glyburide was becoming a mainstay of therapy for type 2 diabetes.

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