Study suggests possible link between two Type 2 diabetes drugs and pancreatic cancer

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Two newer drugs used to treat Type 2 diabetes could be linked to a significantly increased risk of developing pancreatitis and pancreatic cancer, and one could also be linked to an increased risk of thyroid cancer, according to a new UCLA study.

Researchers from the Larry L. Hillblom Islet Research Center at UCLA examined the U.S. Food and Drug Administration's database for adverse events reported between 2004 and 2009 among patients using the drugs sitagliptin and exenatide. They found a six-fold increase in the odds ratio for reported cases of pancreatitis with these drugs, compared with four other diabetes therapies they used as controls. They also found that patients who took the two drugs were more likely to have developed pancreatic cancer than those who were treated with the other therapies.

The study is published in the journal *Gastroenterology*.

"We undertook these studies because several studies in animal models by several investigators had suggested that this form of therapy may have unintended actions to promote growth of the ducts (tubes) in the pancreatic gland that convey digestive juices from the pancreas to the gut," said Dr. Peter Butler, director of the Hillblom Center and a study co-author. "This is a concern if it happens in humans since it might be expected to increase the risk for pancreatitis and pancreatic cancer. While the FDA data base has limitations, it does have advantages in being very large, openly accessible and independent from companies that market the drugs.

"Taken together the animals studies and the FDA data base analysis suggest that further work needs to be undertaken to at least rule out that this now widely available new drug class for diabetes does not increase the risk of pancreatic cancer," Butler, who is also a member of UCLA's Jonsson Comprehensive Cancer Center, added.

Sitagliptin and exenatide are drugs that enhance the actions of a gut hormone known as glucagon-like peptide 1 (GLP-1), which has been shown to be effective in lowering blood sugar in individuals with Type 2 diabetes. Sitagliptin, marketed as Januvia by Merck & Co. Inc., works by inhibiting dipeptidyl peptidase-4 (DDP-4), an enzyme that degrades GLP-1. Exenatide, manufactured by Amylin Pharmaceuticals and sold as Byetta, mimics the action of GLP-1 and resists DDP-4 degradation.

Previous research by UCLA Hillblom Center researchers suggested there might be a link between drugs that enhance the actions of GLP-1 and pancreatitis, possibly resulting from an increase in the rate of formation of cells that line the pancreatic ducts. That research, based on studies in rats, was published in 2009 in the journal Diabetes.

In addition to the six-fold increase in reported cases of pancreatitis, the researchers also found a 2.9-fold greater rate of pancreatic cancer in patients using exenatide and a 2.7-fold higher rate of pancreatic cancer in patients on sitagliptin, compared with the other therapies. Additionally, they found a statistically significant increase in the risk of thyroid cancer among the exenatide group, but not among the sitagliptin group.

The FDA data did not indicate links between the two diabetes drugs and any other form of cancer.

The researchers caution that the FDA's adverse events database "is not the ideal mechanism to compare adverse event rates between drugs,"

given its known limitations, such as incomplete data and reporting biases. They stress that more study is needed.

"Randomized, controlled clinical trials remain the gold standard for such assessment," the researchers wrote.

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