MedicalXpress

Popular diabetes treatment could trigger pancreatitis, pancreatic cancer

April 30 2009, By Enrique Rivero

A drug widely used to treat Type 2 diabetes may have unintended effects on the pancreas that could lead to a form of low-grade pancreatitis in some patients and a greater risk of pancreatic cancer in long-term users, UCLA researchers have found.

In a study published in the online edition of the journal *Diabetes*, researchers from the Larry L. Hillblom Islet Research Center at UCLA found that sitagliptin, sold in pill form as Januvia, caused abnormalities in the pancreas that are recognized as risk factors for pancreatitis and, with time, pancreatic cancer in humans. Januvia is marketed by Merck & Co. Inc. Sitagliptin is a member of a new class of drugs that enhance the actions of the gut hormone known as glucagon-like peptide 1 (GLP-1), which has been shown to be effective in lowering blood sugar in people with Type 2 diabetes.

"Type 2 diabetes is a lifelong disease — people often take the same drugs for many years, so any adverse effect that could over time increase the risk for pancreatic cancer would be a concern," said Dr. Peter Butler, director of the Hillblom Center and the study's lead investigator. "A concern here is that the unwanted effects of this drug on the pancreas would likely not be detected in humans unless the pancreas was removed and examined."

An observed connection between Byetta, a drug used to treat Type 2 diabetes that is related to Januvia in its intended actions, and pancreatitis has already been reported, prompting a Food and Drug Administration

warning. Amylin Corp., which markets Byetta, has suggested that since there is no known mechanism linking the cases of pancreatitis with Byetta, the association might be chance. The UCLA study suggests that there may indeed be a link between drugs that enhance the actions of GLP-1 and pancreatitis — by increasing the rate of formation of cells that line the pancreatic ducts.

In the study, researchers used human IAPP transgenic (HIP) rats to test both sitagliptin and metformin; metformin, a member of an older, different class of diabetes drugs in use since the 1950s, has recently been found to have anti-tumor properties. The researchers sought to determine how the drugs, both singly and in combination, affected islet disease progression in the pancreas — particularly how they affected beta cells in the pancreas's Islets of Langerhans. Beta cells are responsible for releasing insulin in people with normal metabolism, but they don't produce insulin in sufficient amounts in diabetes patients. HIP rats approximate both the islets and metabolism of people with Type 2 diabetes. The drugs were tested in 40 rats for 12 weeks.

The researchers found that the two drugs in combination had a synergistic effect that helped preserve beta cells, improved their function and enhanced insulin sensitivity in the test rats. With the sitagliptin alone, however, the rats had abnormally high rates of cell production in their pancreatic ducts; a few developed an abnormality known as ductal metaplasia, and one developed pancreatitis.

But the metformin, trade name Glucophage, seems to counteract sitagliptin's adverse effect.

"The apparent protection against the unwanted actions of sitagliptin in the exocrine pancreas are intriguing and may offer a potential way of using the GLP-1 class of drugs safely," Butler said. "The protective effect may have been either by the actions of metformin to decrease

blood glucose values or its recently appreciated properties as a tumor suppressive agent."

Butler noted that the present study was undertaken in rats and that it is possible the adverse effects observed would not occur in humans.

"Given these findings, it is probably sensible to use the GLP-1 class of drugs only with metformin until other data is forthcoming," he said.

The National Institutes of Health, the Larry Hillblom Foundation and the Merck Research Foundation funded this study.
More information: The study is available at diabetes.diabetesjournals.org/cgi/content/abstract/db09-0058v1" target="_blank">diabetes.diabetesjournals … abstract/db09-0058v1 .

Provided by University of California Los Angeles (news : web)