Brief Communication

Acute pancreatitis with gliptins: Is it a clinical reality?

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ABSTRACT

There are reports of acute pancreatitis with the use of dipeptidyl peptidase-4 inhibitors (gliptins). This class of drugs is widely being prescribed for type 2 diabetes mellitus (DM) in our country. We evaluated the incidence of acute pancreatitis with the use of gliptins during the period January 2012-June 2013. Patients of type 2 DM on treatment with any of the gliptins (Sitagliptin, vildagliptin, or saxagliptin) for at least 1 month duration were included. A total of 185 patients were included (205.3 patient years of follow-up). Five of them had history of acute pancreatitis (all mild) >6 months prior to inclusion with complete resolution and no chronic pancreatitis. One patient (0.48 per 100 patient years) presented with mild acute pancreatitis which resolved in 8 days. Asymptomatic elevation of serum amylase > 3x upper limit of normal was noted in five patients (2.4 per 100 patient years), without any sonological evidence of pancreatitis, which resolved on withdrawal of gliptins. None of the patients with previous history of pancreatitis had a recurrence of pancreatitis. In a group at low risk of acute pancreatitis, incidence of acute pancreatitis is low with the use of gliptins.

Key words: Dipeptidyl peptidase-4 inhibitors, gliptins, incretin, pancreatitis

INTRODUCTION

Dipeptidyl peptidase-4 inhibitors (gliptins) are effective drugs in management of type 2 diabetes mellitus (DM). There are reports implicating them in causing acute pancreatitis, chronic pancreatitis, and pancreatic duct metaplasia; leading to widespread concern.[1,2] Although gliptins are increasingly being used in clinical practice, data on incidence of acute pancreatitis with this class of drug is lacking from our country. We evaluated the extent of this adverse effect in patients on gliptins on our follow-up.

MATERIALS AND METHODS

This study was conducted as a prospective, observational study in a tertiary care hospital setting. Patients with type 2 DM receiving one of the gliptins (Sitagliptin, vildagliptin, or saxagliptin) for at least 1 month during the study period January 2012-June 2013 were included in the study. Equivalent doses of these three gliptins were used interchangeably during the period of the study depending on their availability in the hospital pharmacy. Detailed history regarding gall stone disease, pancreatitis, alcohol abuse, and drug use was obtained. Relevant clinical examination including anthropometry was done. Five of them had history of acute pancreatitis (all mild) >6 months prior to inclusion which had completely resolved with no residual pseudocyst or chronic pancreatitis. During that episode, these patients were not on treatment with gliptins. In addition to testing fasting and postprandial glycemia; lipid profile, liver and kidney function test, serum amylase, and ultrasonography (USG) of abdomen was done focused at gall stone/sludge, pancreatic morphology, and calcification. Patients were followed-up every month as is the practice at this center. All other tests were done as laid down in relevant guidelines for type 2 DM during follow-up. Patients were explained regarding symptoms of acute pancreatitis (abdominal pain, nausea, and vomiting) and asked to report immediately to nearest medical help if it occurred. Serum amylase test was done immediately at clinical presentation and USG abdomen was
performed. Acute pancreatitis was diagnosed based on raised serum amylase levels ($>3 \times$ upper limit of normal (ULN)) with or without ultrasonographic changes in a patients with symptoms suggestive of acute pancreatitis. In asymptomatic patients, serum amylase and USG abdomen was performed every 3 months to exclude silent acute/chronic pancreatitis. Severity of pancreatitis was assessed based on APACHE scoring system. Patients with history of gall stone disease, chronic pancreatitis, alcohol abuse ($>10$ g daily), consuming drugs known to cause pancreatitis (glucocorticoids, antiretroviral therapy, azathioprine, valproic acid, furosemide, etc.), and hypertriglyceridemia (triglyceride $>1,000$ mg/dl) were excluded. Patients who developed acute pancreatitis were withdrawn from the study, gliptins were discontinued and they were managed on the standard lines for acute pancreatitis based on its severity.

**Results**

A total of 216 patients with type 2 DM on treatment with one of the gliptins for at least 1 month prior to inclusion in the study were seen during the period of the study. Thirty-one patients were excluded based on the set exclusion criteria (gallbladder stone/sludge in 15, alcohol abuse in nine, drug use in five, and triglyceride levels $>1,000$ mg/dl in two patients). Of the remaining 185 patients who were included, 26 were obese (body mass index (BMI) $\geq 25$ kg/m$^2$) and 43 overweight (BMI: 23-24.9 kg/m$^2$). Total follow-up during the study period (number of monthly visits $\times$ number of patients) was 2,464 patient-months (205.3 patient-years). Total duration of gliptin use varied from 1 month to 4 years in these patients (median usage 22 months). During the study period, one patient (0.48 per 100 patient-years) presented with acute abdomen with raised amylase levels in diagnostic range for acute pancreatitis. USG was suggestive of mild acute pancreatitis. He had been on gliptin for 15 months. He recovered completely in 8 days after drug withdrawal. Asymptomatic elevation of serum amylase ($>3 \times$ ULN) was noted in five patients (2.4 per 100 patient years), without any sonological evidence of pancreatitis, which resolved within 3 days of withdrawal of gliptins. None of the patients with previous history of pancreatitis had a recurrence of pancreatitis. As the three available gliptins were used interchangeably by patients during the study period, no particular drug could be implicated in the causation of this adverse effect.

**Discussion**

In this observational study, we noted one patient with acute pancreatitis (an incidence of 0.48 per 100 patient-years) which was mild and self-limiting on drug withdrawal. During the same period, five cases of asymptomatic hyperamylasemia with no sonological evidence of pancreatic inflammation were noted. None of the patients developed chronic pancreatitis during the study period.

Incidence of acute pancreatitis in general population is reported to be around 1.9 per 1,000 patient years and is known to occur at a greater frequency in patients with diabetes (5.6 per 1,000 patient years). This risk has been shown to be similar or up to six-folds higher in various observational studies with glucagon-like peptide 1 based therapies. Although drug-induced pancreatitis can occur at any duration of exposure, more than half of gliptin associated acute pancreatitis has been reported to occur in the first month of exposure. Gliptins are also implicated in causing silent chronic pancreatitis, but none was noted in our patients during the period of follow-up.

The limitations of this study are patient self-reporting of symptoms of acute pancreatitis, which often may be mild and ignored by the patient. Alcohol abuse of even less than the exclusion criteria used in this study may cause or contribute to acute pancreatitis. Only USG was used for imaging of the pancreas due to ease of performing and safety although CT scan is a better modality for pancreatic imaging. This might have missed a few cases of mild acute pancreatitis. Amylase levels return to baseline within 48 h of onset of symptoms, hence delayed presentation may have led to a false negative normal amylase. More patients with asymptomatic hyperamylasemia might have been missed as screening was done quarterly.

To the best of our knowledge, this is first report of incidence of acute pancreatitis with use of gliptins from India. Larger prospective database with a diabetic and nondiabetic control population is likely to shed more light on this issue.

**Conclusion**

Acute pancreatitis is well known to occur at a greater frequency in patients with type 2 DM. The heightened risk of this dreaded disease is suspected with the use of gliptins. In this small study with its limitations, we did not note any greater risk of acute pancreatitis than expected in a cohort of type 2 DM patients. However, greater watchfulness for this dreaded adverse effect and avoidance of its usage in patients at high risk for pancreatitis is a prudent approach.

**References**

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