Treatment with DPP-4 Inhibitors does not Increase the Chance of Pancreatitis in Patients with Type 2 Diabetes

Ananth Samith Shetty*, Arun Nanditha†, Chamukuttan Snehalatha**, Ambody Ramachandran***

Abstract

Objectives: This retrospective analysis was done in type 2 diabetes patients to study whether treatment with either sitagliptin or other Dipeptidyl peptidase-4 (DPP-4) inhibitors increased the risk of pancreatitis. Comparison with patients treated with other Oral Antidiabetic Drugs (OADs) was done.

Methods: Asian Indian type 2 diabetic subjects (duration ≥ 5 years) treated with sitagliptin or other DPP-4 inhibitors (n=957) were selected from the clinic records. Control group included patients treated with other hypoglycaemic agents and had serum lipase and/or amylase estimated (n=718). HbA1c and serum levels of lipase and/or amylase were measured. For lipase, values ≥ 90 IU/l and for amylase, values ≥ 150 IU/l were considered abnormal.

Results: Percentages with elevated lipase values were similar among patients on sitagliptin or other gliptins and control subjects. Similar percentages of patients using DPP-4 inhibitors (6.9%) or other hypoglycaemic agents (8.2%) had elevated levels of lipase. Abnormal amylase values were more common among the control subjects vs those using DPP-4 inhibitors.

Conclusions: Present analysis suggests that use of DPP-4 inhibitors is safe in patients who do not have contraindications for its use.

Introduction

Dipeptidyl peptidase-4 (DPP-4) inhibitors prevent degradation and prolong the action of endogenous incretin hormones. The main advantages of using DPP-4 inhibitors over the other available antidiabetic agents are that it enhances biologically active glucagon like peptide (GLP-1), increase insulin secretion and suppresses glucagon secretion in a glucose dependent manner, and they are weight neutral. Since the increase in beta cell function is glucose-dependent, very low rate of hypoglycemia are seen.1-3 A major beneficial effect noted is the improvement of beta cell function and beta-cell mass although these have been demonstrated mainly in animal models.4 Currently more than 10 different DPP-4 inhibitors have either been used or are being evaluated by different pharmaceutical companies.

Sitagliptin was the first DPP-4 inhibitor that was approved for the management of type 2 diabetes in 2007. Sitagliptin is being used as monotherapy (100 or 200 mg OD) or as an add-on to ongoing oral antidiabetic agents (OAD) in patients with type 2 diabetes with significant reduction in glycaemic levels within a few weeks.5

Though gliptins have been found to be highly effective oral agents in reducing hyperglycaemia, there have been concerns about its potential to increase the chances of pancreatitis.6

The aim of this study was to analyse whether the use of DPP-4 inhibitors produce biochemical changes suggestive of pancreatitis in type 2 diabetic patients. This retrospective analysis was done in a group of type 2 diabetes patients who had been treated with either sitagliptin or other DPP-4 inhibitors in combination with other drugs, for a minimum period of 6 months, and a comparison was done with a group of patients treated only with other hypoglycaemic agents.

Materials and Methods

The study group of 957 Indian type 2 diabetic subjects treated with sitagliptin or other DPP-4 inhibitors was selected from the clinic records of a tertiary care hospital for diabetes. As the control group, type 2 diabetes subjects treated with other hypoglycaemic agents (non-incretin based therapy) and who also had serum lipase and / or amylase estimated (n=718) were selected.

The dose of sitagliptin or vildagliptin used was 100mg/day and that of saxagliptin was 5mg/day.

Patients with chronic alcoholism were excluded from the study. All patients had ≥ 5 years of duration of diabetes and had been on treatment. The patients using DPP-4 inhibitors were on the drug for a minimum of 6 months. The selected subjects had measurements of HbA1c and serum levels of lipase and / or amylase. Nearly 60% of them had serial estimations of the enzymes. The highest value among the estimations was used in

<table>
<thead>
<tr>
<th>Variables</th>
<th>Control</th>
<th>Sitagliptin</th>
<th>Other gliptins</th>
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</thead>
<tbody>
<tr>
<td>HbA1c (%)</td>
<td>8.5 ± 1.7</td>
<td>8.9 ± 1.6a</td>
<td>9.1 ± 1.6a</td>
</tr>
<tr>
<td>Lipase (IU/l)</td>
<td>53.1 ± 35.4</td>
<td>52.6 ± 26.6</td>
<td>50.8 ± 24.4</td>
</tr>
<tr>
<td>Amylase (IU/l)</td>
<td>76.3 ± 36.9</td>
<td>70.6 ± 31.8</td>
<td>68.1 ± 29.0</td>
</tr>
</tbody>
</table>

Control vs Sitagliptin – a=p<0.0001, b=p=0.002; Control vs Other gliptins – a=p<0.0001

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this analysis. Patients were considered to have increased levels of lipase (≥ 90 IU/l) and amylase (≥ 150 IU/l) if the values were higher by 1.5 times of the upper limit of normal, which was a conservative approach.

HbA1c was analysed by an immunoturbidimetric method, using TinaQuant II reagents of Roche Diagnostics, Germany. Serum amylase and lipase were also done using the reagents of Roche diagnostics on Cobas Integra autoanalyzer (Roche Diagnostics).

Comparisons were done between the subjects who were treated with sitagliptin, other gliptins and control group using appropriate statistical tests such as Students’ ‘t’ test or the chi-square test.

Results

Table 1 shows the characteristics of the study groups. Patients on DPP-4 inhibitors were younger and had shorter duration of diabetes than the control group. Mean HbA1c was significantly higher among the patients treated with gliptins other than sitagliptin. Mean amylase values among the groups treated with gliptins were significantly lower than in the control group.

Percentages of patients with elevated lipase values were similar among the three groups studied. Percentage with increased levels of amylase was higher in the control group than in the groups treated with gliptins (Table 2).

Two cases of acute pancreatitis were detected in our hospital, both cases were being treated with vildagliptin. Detailed study of the two cases showed that the patients had evidence of chronic pancreatitis, even before initiation of treatment with DPP-4 inhibitor. They had extremely high levels of pancreatic enzymes and also had evidence of chronic pancreatitis by ultra sonography. These cases have been excluded from the calculation due to skewed nature of the enzyme values.

Discussion

The study showed that prevalence of elevated pancreatic enzymes suggestive of pancreatitis, was similar in type 2 diabetes patients being treated with DPP-4 inhibitors or with other hypoglycaemic agents. In this study, 6.9% of the patients using DPP-4 inhibitors had elevated levels of lipase vs 8.2% of control group. The difference was not statistically significant. Presence of elevated amylase was significantly higher among the control subjects vs those using DPP-4 inhibitors.

In this study, we had used a lower conservative cutoff for elevated levels of the enzymes so that even borderline changes could be picked up.

In a retrospective study of a large medical and pharmacy clinical data base in the USA, Garg et al. found that acute pancreatitis was significantly higher in the diabetic subjects than in the non-diabetic control group. However, the risk of acute pancreatitis was similar in the exenatide vs diabetic control group and sitagliptin vs diabetes control group. The control subjects had used medication other than exenatide or sitagliptin. Therefore it was concluded that the possibility of an increased risk of acute pancreatitis with use of exenatide or sitagliptin was limited. Dore et al. also did not find that the risk of pancreatitis was increased either with exenatide or with sitagliptin.

Present analysis suggests that use of DPP-4 inhibitor is safe provided they are used in patients who do not have contraindications for their use.

Acknowledgement

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References


Table 2: Prevalence of elevated enzyme levels

<table>
<thead>
<tr>
<th>Abnormal</th>
<th>Control (n=718)</th>
<th>Sitagliptin (n=634)</th>
<th>Other gliptins (n=323)</th>
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<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>Lipase</td>
<td>59</td>
<td>8.2</td>
<td>41</td>
</tr>
<tr>
<td>Amylase</td>
<td>30</td>
<td>4.2</td>
<td>14</td>
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</tbody>
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*p=0.046 Vs Control.