EXENATIDE ADD TO METFORMIN- THE EVIDENCE FOR ACHIEVING GLYCEMIC CONTROL IN TYPE 2 DIABETES

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ABSTRACT: The treatment options for type 2 diabetes mellitus (T2DM) have increased significantly over the past 10 to 15 years. Incretin hormones, which are found in the gastrointestinal system and other tissues, are integral to glucose homeostasis, increasing insulin secretion, reducing glucagon secretion, slowing gastric emptying, and enhancing early satiety. Enhancement of the incretin system with GLP-1 (glucagon like peptide 1) receptor agonists and DPP-4 (dipeptidyl peptidase 4) is effective in reestablishing glucose homeostasis. Exenatide, a twice-daily injectable GLP-1 receptor agonist, was approved in 2005 by the FDA for the treatment of type 2 diabetes mellitus (T2DM). The author suggests to evaluate the efficacy and safety of exenatide in patients with T2DM not adequately controlled with metformin (1500-2500 mg/d); primary endpoint: HbA1C (glycosylated hemoglobin) change after 48 weeks, secondary endpoint: fasting plasma glucose, postprandial glucose, body weight change, hypoglycemia, adverse events. The study was conducted on the Emergency Clinical County Hospital of Arad, Diabetes Mellitus Department, during June 2011-July 2012 and comprises 24 patients admitted in the hospital for diabetological disorders, treat with metformin 1500-2500 mg daily.

KEYWORDS: incretin effect, DPP-4, GLP-1, GIP, exenatide

INTRODUCTION

Exenatide (Byetta, Amylin Pharmaceuticals, Inc), a GLP-1 receptor agonist, is the first drug in this class to be approved by the FDA and marketed in the United States. It has been approved as an adjunctive therapy for use in patients with T2DM who take metformin, a sulfonylurea, a thiazolidinedione, a combination of metformin and a sulfonylurea or a combination of metformin and a thiazolidinedione). Exenatide is derived from exendin-4, which is found in saliva of the Gila monster and is 53% homologous to human GLP-1; exenatide is less susceptible to DPP-4 degradation than is native GLP-1, and it has a mean half-life of 2.4 hours, compared with about 2 minutes for native GLP-1 (glucagons like peptide 1).

OBJECTIVES

The author suggests to evaluate the efficacy and safety of exenatide in patients with type 2 diabetes mellitus not adequately controlled with metformin. Primary endpoint: HbA1C change after 48 weeks; Secondary endpoint: fasting plasma glucose, postprandial glucose, body weight change, hypoglycemia, adverse events.

RESEARCH DESIGN AND METHODS: The study was conducted on the Emergency Clinical County Hospital of Arad, Diabetes Mellitus Department, during June 2011-July 2012 and comprises 24 patients admitted in the hospital for diabetological disorders, treat with metformin 1500-2500 mg daily.

Inclusion criteria:
- type 2 diabetes as defined by the American Diabetes Association;
- baseline HbA1c between 7 and 10%;
- patients having received stable doses of metformin before randomization (patients with type 2 diabetes on metformin for at least 3 months and have been on a stable dose of metformin of at least 1500 mg daily for a minimum of 4 weeks);
- fasting plasma glucose <220 mg/dl;
- agreement to maintain the same dose of metformin throughout the study;
- agreement to maintain prior diet and exercise habits during the full course of the study.

Exclusion criteria:
- a history of acute metabolic diabetic complications;
- evidence of significant diabetic complications;
- insulin treatment for longer than 10 days within the past 6 months;
- treatment with any oral anti-diabetic other than metformin.

Characteristic subjects:
- age (years): 42-60;
- sex: male- 9(37,5%) and female- 15(62,5%);
- body mass index (kg/m2): 30,5-37;
- duration of diabetes mellitus (years):4-11;
- HbA1c at screening: 7-10%;

Patients who had an HbA1c (hemoglobin glycate) >10% or fasting glucose value >220 mg/dl were not eligible to be randomized. The mean baseline HbA1c was 8,2%.

**RESULTS**

Coadministration exenatide 10mg daily(twice) and metformin 1500-2500 mg daily provided significant improvements in HbA1c.

Fasting plasma glucose changes from baseline (mean baseline 162mg/dl) were -22mg/dl; postprandial plasma glucose changes from baseline (mean baseline 187mg/dl) were -55mg/dl(fig.1).

**Fig.1 PLASMA GLUCOSE CHANGES FROM BASELINE**

<table>
<thead>
<tr>
<th>GBI</th>
<th>GBF</th>
<th>GPPi</th>
<th>GPPF</th>
<th>GMI</th>
<th>GMF</th>
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<td>162</td>
<td>140</td>
<td>187</td>
<td>137</td>
<td>171</td>
<td>137</td>
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**GMI = 171 MG/DL (MEAN BASELINE PLASMA GLUCOSE)**

**GMF = 137 MG/DL (AT 48 WEEKS MEAN PLASMA GLUCOSE)**

Greater reduction in HbA1c was associated with higher baseline HbA1c.

From a mean baseline of 8,2%, changes from baseline were-0,95%(fig.2).

**Fig.2 HbA1c reduction after 48 weeks**

The proportion of patients achieving an HbA1c<6,5% was 33%, but for 63% the addition of exenatide provided HbA1c lowering<7% (fig.3).

**Fig.3- Greater proportions of patients achieved HbA1c target**

- **HbA1c<6,5%**
- **HbA1c 6,5-7%**
- **HbA1c>7%**
Fasting plasma glucose changes from baseline (mean baseline 162mg/dl) were -22mg/dl; postprandial plasma glucose changes from baseline (mean baseline 187mg/dl) were -55mg/dl (fig.3).

Finally, homeostasis model assessment-beta cell function (HOMA beta) was calculated in 20 patients who finished the study, with HOMA Calculator Version 2.2.2. available at http://www.dtu.ox.ac.uk/homa (was measured C-peptide level initial and after 48 weeks, respectively fasting plasma glucose level). Homa beta was significantly improved: 15.5%. (fig.4).

Fig.4 HOMA beta changes

58.3% patients reported gastrointestinal symptoms (nausea, diarrhea or abdominal pain). There were 2 patients who reported hypoglycemia symptoms. At 48 weeks the mean of body weight was significant reduced (3.25kg). Another benefit from long-term dosing with exenatide was an improvement in cardiovascular risk factors when compared to baseline (fig 5).

Fig. 5 Coadministration exenatide 10mg daily(twice) and metformin provided an improvement in cardiovascular risk factors

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