

Marked Improvement in Glycemic Control with Exenatide on Addition to Metformin, Sulfonylurea and Insulin Glargine in Type 2 Diabetes Mellitus, a Real World Experience

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Abstract

Background: The major effect of Exenatide is attributed to lowering of post-prandial glycemia, whereas insulin glargine mainly improves fasting glycemia [FPG]. **Objective:** Therefore, we assessed effect of Exenatide administration at 6 months and for at 1 year on glycemic control, lipids, body weight [BW], daily insulin dose and hypoglycemic events. **Methods:** Records of 164 subjects, 126 men and 38 women administered Exenatide between January 2011 and December 2013 are included in this report. Exenatide was initiated at 5 mcg subcutaneously twice daily [BID] in obese subjects, BMI > 30 kg/m², with C-peptide > 1 ng/d, and HbA1c 7.5% - 9.5%, while receiving daily metformin 2000 mg, Sulfonylurea Glimepiride 8 mg and insulin Glargine [GLAR]. **Exclusion criteria** were creatinine > 1.5 mg/dL and liver enzymes > 2.5 times upper limit of normal. **Indices of glycemic control** include fasting plasma glucose levels and HbA1c. **Lipids** include serum concentrations of total, LDL and HDL cholesterol. **Other endpoints** are body weight, daily insulin dose and number of hypoglycemic events per patient during 4 weeks prior to initiation of Exenatide, at 6 months and 1 year of therapy. **Results:** In 37 subjects, Exenatide was discontinued within 1 - 3 weeks; 29 due to onset of nausea and vomiting. Seven of these also complained of abdominal pain and in these, serum amylase and lipase were elevated indicating presence of acute pancreatitis. One subject discontinued because of chest pain. Fasting plasma Glucose remained unchanged following Exenatide administration. However, HbA1c declined significantly denoting improvement in overall glycemic control without significant changes in body weight, daily insulin

dose and hypoglycemic events. Lipid panel improved as well. Conclusion: Exenatide may be an appropriate adjuvant option in obese subjects with Type 2 diabetes mellitus with lack of desirable glycemic control while receiving therapy with Metformin, Glimepiride, and insulin Glargine. Moreover, improvement in glycemic control is likely to be secondary to lowering of post prandial hyperglycemia induced by Exenatide.

Keywords

Type 2 Diabetes Mellitus, Glycemic Control, Insulin Glargine, Metformin, Sulfonylurea, Exenatide

1. Introduction

Exenatide is an incretin mimetic, having glucoregulatory activities similar to those of naturally occurring mammalian hormone GLP-1 secreted by L cells lining the ileum and jejunum in response to meal [1] [2] [3]. GLP1 enhances glucose-dependent insulin secretion by beta cells while simultaneously inhibiting glucagon release by alpha cells both residing in pancreatic islets [2]-[7]. Moreover, exenatide delays gastric emptying [2]-[7]. Finally, data in animal models as well as humans indicate that both native GLP1 and GLP1 receptor agonists cause weight loss by reducing food intake via stimulation of satiety center [8]-[14]. However, Exenatide has a greater potency and a longer duration of action in comparison to the native GLP-1 when administered subcutaneously [4].

The major effect of Exenatide in improving glycemic control in subjects with type 2 diabetes is attributed to lowering of post-prandial glucose [PPG] concentration [9]-[17]. Therefore, we examined the effect of administration of Exenatide on indices of glycemic control in subjects with type 2 diabetes with desirable fasting plasma glucose levels, but still elevated HbA1c concentrations while receiving insulin Glargine, Glimepiride and Metformin.

2. Subjects and Methods

Data was collected retrospectively by examining the records of 164 obese subjects, 126 men and 38 women with type 2 diabetes attending diabetes clinics at 2 academic medical centers during a period of 6 years between January 2011 and December 2016. The study protocol was approved by Institutional Review Boards at both medical centers. The major inclusion criterion was the records of subjects in whom therapy with Exenatide was initiated because of failure in attaining desirable HbA1c levels < 7.0% as recommended by American Diabetes Association [18] despite achieving desirable fasting plasma glucose concentrations, 90 - 130 mg/dl while receiving p maximum daily dose of Glimepiride, 8 mg; Metformin 1000 - 2000 mg as tolerated and insulin Glargine administered subcutaneously in AM. The other inclusion criteria were obesity with BMI > 30 kg/m², C-peptide > 1 ng/dl, HbA1c levels ranging between 7.5% - 9.0% at initia-

tion and minimum duration of 1 year while receiving combination therapy. This range of HbA1c was chosen because post prandial glycemia is documented to be a major contributor to this range of HbA1c levels [19]. Moreover, fasting plasma glucose in the desirable range of 80 - 130 mg/ dl confirms the contribution of post prandial hyperglycemia to elevated HbA1c levels in subjects included in this study. Exclusion criteria were serum creatinine levels > 1.5 mg/dL and liver enzymes > 2.5 times upper normal limit.

Adjunctive therapy with Exenatide was elected because the major effect of Exenatide is well established to lower post prandial hyperglycemia [9]-[17]. Exenatide was administered subcutaneously with initial dose, 5 mcg twice daily prior to breakfast and supper. The dose was increased to 10 mcg twice daily after 2 - 4 weeks if the initial dose was tolerated without nausea, vomiting, diarrhea or abdominal pain. Concomitant therapy with same oral agents; metformin, Glimpiride and insulin Glargine was continued for at least one year. The daily dose of insulin Glargine was adjusted as required on onset of hypoglycemia as documented by presence of symptoms accompanied by blood glucose level < 60 mg/dl determined by self blood glucose monitoring. Data includes indices of glycemic control e.g. HbA1c, fasting plasma glucose levels as well as serum concentrations of total, LDL and HDL cholesterol, urea nitrogen, creatinine and liver enzymes. Daily insulin dose, body weight and all other parameters were determined prior to initiation of Exenatide and again at 6 months and 1 year. Number of hypoglycemic events during 4 weeks prior to initiation of Exenatide and at the end of 1 year of therapy is reported as well. Comparisons between glycemic and other outcomes prior to initiation of exenatide and at 6 months and 1 year following the adjunctive therapy were conducted by statistical analyses using Student's "t" test and analysis of variance.

3. Results

Population comprised 164 adult subjects, 126 men and 38 women with ages, 34 - 72 years. Diagnosis of type 2 Diabetes was established by documentation of desirable glycemic control while receiving oral agents for several years as well as fasting c-peptide concentration > 1 ng/dl. Duration of diabetes ranged between 8 - 20 years. 127 subjects were noted to complete a year of combination therapy (77%) whereas in 37 subjects (23%), Exenatide was discontinued within 1 - 3 weeks; in 36 subjects because of onset of abdominal pain and/or nausea and/or vomiting. In 7 of these subjects, further evaluation revealed elevated serum amylase and lipase levels indicating presence of acute pancreatitis. One subject discontinued because of chest pain. Thus, Exenatide was withdrawn soon after initiation because of onset of adverse event.

Fasting plasma glucose concentrations remained between 80 - 130 mg/dl in all subjects (Table 1). However, HbA1c levels declined in all subjects by 6 months and lower concentrations were maintained at 1 year (Table 1). Desirable HbA1c concentration < 7% was attained and maintained in 87% of subjects while remaining subjects achieved HbA1c levels below 7.6%.

Table 1. Fasting Plasma Glucose (FPG), HbA1c, lipid panel, body weight, daily insulin dose and hypoglycemic events per patient during 4 weeks prior to initiation (pre Rx) and again at 6 months and 1 year after (post Rx) treatment with Exenatide.

	PreRx	PostRx 6 months	Post Rx 1 year
FPG (mg/dl)	112 ± 6	105 ± 5	109 ± 8
HbA1c (%)	8.1 ± 0.2	6.7 ± 0.1*	6.8 ± 0.1*
Total Cholesterol (mg/dL)	152 ± 12	129 ± 10	125 ± 9†
Triglycerides (mg/dL)	269 ± 41	205 ± 38	198 ± 36*
HDL (mg/dL)	35 ± 2	38 ± 3	37 ± 3
LDL (mg/dL)	80 ± 16	75 ± 11	81 ± 10
Body weight (kg)	134 ± 7	138 ± 8.	135 ± 9
Insulin (units/day)	101 ± 22	93 ± 19	96 ± 18
Hypo G/patient	2.3 ± 0.4	1.9 ± 0.6	2.1 ± 0.5

*p < 0.01 vs Pre Rx, †p < 0.05 vs Pre Rx.

Serum cholesterol and triglyceride levels declined by 6 months with improvement being maintained at 1 year while no significant alterations were documented in LDL and HDL cholesterol concentrations (**Table 1**).

Mean body weights prior to initiation of Exenatide and at 6 months and 1 year following therapy were not significantly different (**Table 1**). However, the change in body weight was not consistent with a weight gain 1 - 3 kg noted in 56 subjects and a weight loss of 0.8 - 2.2 kg in the remaining 72 subjects. Finally, mean daily insulin glargine dose appeared to decline on addition of Exenatide (**Table 1**). However, daily doses at initiation of Exenatide and at 6 months and 1 year following treatment were not significantly different (**Table 1**). Finally, hypoglycemic events during last 4 weeks of both phases of treatment, prior to initiation of Exenatide and at the end of 1 year were not significantly different (p > 0.10).

4. Discussion

This study documented exenatide withdrawal due to onset of established adverse effects of intolerable abdominal pain, nausea or vomiting in 22.6% of subjects. Moreover, acute pancreatitis occurred in 7 of 127 subjects. Both these observations are consistent with previous data in several studies [11]-[17] [20].

This study also demonstrates that in subjects with type 2 diabetes, addition of exenatide to background therapy consisting of Metformin, Sulfonylurea and basal insulin glargine leads to marked improvement in glycemic control as expressed by a significant lowering in HbA1c (**Table 1**). This finding is consistent with previous data in the literature including several clinical trials [11]-[17]. Improvement in glycemic control with lowering of HbA1c may be attributed to reduction in post prandial hyperglycemia since fasting plasma glucose concentrations were unchanged. Moreover, major physiologic effect of exenatide in lowering post prandial glycemia via stimulating insulin secretion and inhibiting

glucagon release is well established [2]-[7]. Finally, the role of lowering of post prandial hyperglycemia in the decline in HbA1c is also consistent with previous documentation of post prandial glycemia being the major contributor to HbA1c levels noted in subjects prior to initiation of exenatide in this study [19].

This study documents mixed results in terms of the lipid panel; a significant reduction in total cholesterol and triglyceride levels with no significant alterations in LDL and HDL cholesterol concentrations. These results are apparently analogous to two other prospective studies [12] [14], although in contrast to another study, it documented decline in the HDL levels following treatment with exenatide [8]. Lowering of total cholesterol and triglyceride levels may be attributed to improvement in glycemic control as previously documented [21] [22] [23] [24] [25].

In this study, significant change in body weight was not documented in subjects as a group. Insignificant weight gain in some subjects and similar weight loss in others may have contributed to this finding. However, this observation is consistent with the data regarding body weight in the original pre-marketing clinical trial [12]. In this trial, marked weight loss documented in subjects continuing exenatide despite experiencing adverse side effects may have contributed to significant decline in mean body weight as minimal change in body weight was evident in other subjects tolerating the drug. Similar significant weight loss was noted in subjects using exenatide in another study [11]. However, data lacked detailed information regarding body weights in individual subjects. The differences in changes in body weights observed in some other studies as well [12] [13] [14] [15]. This inconsistent findings regarding changes in body weights may be attributed to the different times during the day at which exenatide was administered coupled with various other factors, such as lack of exercise or sedentary lifestyle. Another potential reason for lack of significant changes in body weight in subjects in this study is the lack of requirement of bed time snack due to almost negligible onset of nocturnal hypoglycemia secondary to administration of insulin Glargine U100 or insulin Glargine U300 in AM as opposed to bedtime documented in previous studies [26] [27] [28] [29]. Weight gain noticed in subjects receiving insulin glargine at bedtime may be due to a consumption of a snack following insulin administration because of the concern of nocturnal hypoglycemia on part of both patients and providers alike especially because of a fairly large dose required by most obese subjects with type 2 Diabetes. Finally, lower daily insulin dose on addition of exenatide noted in this and other studies may contribute to lack of weight gain as well [11]-[17].

In final analysis, in patients with type 2 DM with poorly controlled glycemic levels while receiving combination treatment with insulin glargine, metformin and Glimperide, addition of exenatide induced a marked reduction in HbA1c, serum cholesterol and triglyceride levels. Moreover, this improvement occurred without both the weight gain and a significant rise in hypoglycemia, a distinct advantage over administration of rapid acting insulin to lower post prandial hyperglycemia. Therefore, addition of exenatide or another GLP 1 receptor

agonist may be preferred to use of rapid acting insulin in subjects with type 2 diabetes with lapse of glycemic control while receiving metformin, Glimepiride and basal insulin Glargine.

However, this study has several limitations including retrospective observational nature, lack of comparisons with either placebo or other oral agents e.g. DPP4 inhibitors or injectable rapid acting insulin, well established strategies for lowering postprandial hyperglycemia. However, the findings are important since use of ezanatide or other GLP1 receptor agonist may be preferential to rapid acting insulin, especially in obese subjects with diabetes because of their beneficial effect on body weight and hypoglycemia. This beneficial effect in terms of hypoglycemia is distinctly crucial in elderly because of frequent presence of hypoglycemia unawareness rendering onset of hypoglycemia detrimental to well being resulting in a seizure, a stroke, acute coronary event, arrhythmia and even death.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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