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Evolution of Biochemical Effects of Byetta® in Type 2 Diabetics with Cardiovascular Risk

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ABSTRACT

The objective of this study was to examine longitudinally the effects of exenatide on different physical and biochemical markers, evaluated in adult type 2 diabetic patients with cardiovascular risk. Data were recorded from 10 patients who attended the outpatient primary care health center Mariano Iago Yecla, Murcia province, Spain in the period of December 2009 to October 2011 and who were treated with Byetta®. Differences were statistically significant ($p < 0.05$) in HbA_{1c} from the third month of treatment, and trends of decrease in body weight from the third week of treatment. There was a significant and better glycemic control. Overall effect was interpreted as a sensitizer drug of the parameters evaluated. Randomized studies are recommended with a minimum follow-up of 2 years, to see if the results are maintained over time.

Keywords: Diabetes Mellitus Type 2; Exenatide; Cardiovascular Risk

1. Introduction

Exenatide (Byetta®, Eli Lilly) is an incretin mimetic, and a synthetic peptide (amide acid peptide of 39 amino acids) which is currently approved in several countries worldwide (marketed since 2006 in the European Union) for use as combination therapy with sulfonylureas and/or metformin in patients with type 2 diabetes mellitus who have not been achieved adequate glycemic control with oral antidiabetic earlier [1,2]. Its therapeutic action is related primarily to reduce both postprandial glucose and fasting, before the consideration of the following four aspects [3-6]:

1) Increased insulin secretion by β cells independently of glucose (reduced insulin release with decreasing blood glucose).

2) Inhibition of glucagon secretion and hepatic gluconeogenesis as well.

3) Slowing of gastric emptying and, consequently, the transition to the movement of glucose intake.

4) Increased satiety.

Exenatide is indicated as an alternative to insulin therapy or other measures of second line therapy in patients with obese type 2 diabetes mellitus in combination with sulfonylurea, metformin or pioglitazone when these options have not achieved adequate glycemic results in a maximum dose [1,7-9].

Exenatide is available as a pre-filled pen of 5 and 10 mg subcutaneous injection administration. We recommend starting the treatment administered 5 mg/2 times/day for 1 month, to increase tolerance. The application is recommended within 60 minutes prior to breakfast and dinner, or two main meals, separated by a minimum of 6 hours, never after a meal. If necessary, to improve glycemic control, the dose may be increased to 10 mg/2 times/day, following the above recommendations of administration [1,2].

The Andalusian Centre of Drug Information (CADIMA) [2] and Campoamor [3], considered high treatment exenatide daily and annual cost (considering the two doses) compared with other treatment options and oral insulin (excluding with liraglutide has a higher cost and annual daily exenatide). In 2009, he referred a daily cost of 4.47 €, maximum value followed by vildagliptin (2.25 €), in-

sulin detemir ornate feathers (2.09 €), insulin glargine cartridges (2.05 €), insulin glargine ornate feathers (2.05 €), pioglitazone (2.03 €) and sitagliptin (2.00 €).

For approved indications, currently controversial information on the effectiveness of exenatide and biochemical markers is associated with physical, being in constant research, the main reason for this study. Despite this, there is some consensus that the administration is associated with a significant reduction in glycosylated hemoglobin levels (HbA_{1c}) and body weight [1,2].

It is also very limited availability of scientific information about its use in obese patients and in combination with other oral agents such as glitazones, as well as on mortality and morbidity and association with cardiovascular risk factors and liver.

It presents a comparative effectiveness not less than insulin. Its use is associated with a high level of withdrawals from treatment due to adverse effects: 8% compared with 3% of placebo and 1% insulin [2]. Among the major adverse effects can be mentioned [1,2,10-14]:

- Nausea (45% - 51%).
- Vomiting (12% - 14%).
- Diarrhea (9% - 17%).
- Hypoglycemic episodes (28% - 36%) in combination with sulfonylureas.
- Acute pancreatitis (89 cases in the European Union in the period 2006-2007).

These effects depend on the continuity of treatment and combination therapy implemented. The truth is that against the perceived benefits of reducing HbA_{1c} and body weight, low risk of hypoglycemia (except in combination with a sulfonylurea), low blood pressure and a potential protective effect of β cells, has the following disadvantages: the administration of injections, frequent gastrointestinal side effects, high costs, little experience in treatment, antibody formation and possible interactions with other drugs given delayed gastric emptying. Regarding the cardiovascular risk associated with diabetes mellitus, there is a current controversy, the effects of exenatide, finding favorable effects [15-21] or on heart rate and blood pressure [15,22,23].

The aim of this study is to contribute to the evolutionary analysis of the effects of exenatide on physical and biochemical markers evaluated in the specific case of adult type 2 diabetic patients with cardiovascular risk.

2. Materials and Methods

Study Design

An experimental study was conducted, longitudinal panel, and quantitative. The scientific data were obtained from medical records of 10 patients with type 2 diabetes mellitus and cardiovascular risk who attended the outpatient primary care health center Mariano Yago in the town of Yecla, Murcia, Spain for the period December 2009 to October 2011.

Physical data were collected: weight, height, shape and body mass index (BMI) and biochemical glycosylated hemoglobin (HbA_{1c}).

We considered three evolutionary breakpoints: 3, 6 and 12 months. Not all participants were evaluated in the cuts, but that they were established considering a unit of group analysis.

Combined treatment with Byetta® was diverse, encompassing various alternatives and combinations, depending on the needs of each patient and medical professional criteria. It included, among others: Januvia 145®, Prevencor 40®, 20® Coropres, Enalapril 20®, Uniket Retard®, add 100®, Glucophage 850® and Actos®.

In all cases reported, as appropriate: time of ingestion. In the case of Byetta®, all patients started the first month with Byetta® 5 mg and two months later switched to 10 mg, always 2 times/day, maintaining this dose in subsequent months.

The glycosylatedhemoglogina biochemical parameter was evaluated according to the criteria for optimal control of the Spanish Society of Diabetes (SED), where:

- $HbA_{1c} \leq 7\%$.

The study was conducted based on various measures of physical and biochemical parameters of 10 adult subjects with type 2 diabetes mellitus and cardiovascular risk. The sample was prepared in a non-probabilistic, intentional and accidental, according to glycosylated hemoglobin detected in the patient's analytic and BMI.

Inclusion criteria for the preparation of the sample were: be patient with diagnosed type 2 diabetes mellitus, adult at the time of diagnosis and treatment.

We excluded cases that did not record a BMI greater than or equal to 30 and type 1 diabetes was based on the discretion of the physician who treated the patient in due course.

Considering the number of subjects, we applied the contrast of the Shapiro-Wilk normality, to inquire about the possibility of parametric analysis tools. All physical and biochemical parameters of analysis, were associated with probabilities >0.05, so that was adopted following a normal statistical distribution.

We analyzed the existence of statistically significant differences in both the temporal evolution of parameters (initial-final, or initial-3-6 to 12 months, as applicable) and months of treatment, by a factor univariate ANOVA (time of measurement).

In cases of biochemical parameters in which such significant differences were found, deepened trying discriminate analysis results according to certain factors, those presented in the overall profile of the participants (except the initial height and weight, used for calculation of initial BMI, and contour). In this case, we applied a

univariate ANOVA on several factors. For categories of factors were considered as follows:

- Age: <57, ≥57, according to 50th percentile.
- Sex: female, male.
- Initial BMI, pre-obesity (25.00 to 29.99 kg/m^2), obesity class I (30 to 34.99 kg/m^2), obesity class II (35.00 to 39.99 kg/m^2) and Class III obesity (≥40.00 kg/m^2) according to the criteria of the World Health Organization (WHO) and the calculation of a minimum of 28.00 kg/m^2 and a maximum of 60.00 kg/m^2.
- Duration of treatment: 3, 6 and 12 months.

Also, in such cases, we analyzed the existence of statistically significant differences by parameter, time and between groups using a univariate ANOVA of a factor.

In the univariate ANOVA was applied on several factors test or Duncan multiple range means separation test as a method of comparing them, in cases in which the categories of factors were more than two.

All analysis was performed with SPSS software version 15.0 for Windows, considering a significance level of $p < 0.05$.

3. Results

The general profile of the patients presented in **Table 1**. In the same average age is observed associated with older subjects, mainly male, obese, and average height.

Table 2 shows the average baseline biochemical INDICATORS evaluated in the study.

In the group treated with Byetta® for 3 months, statistically significant differences ($p < 0.05$) in HbA_{1c} parameter ($F_{1.10} = 7.531$, $p = 0.021$). In this case, we found a significant decrease in the indicator towards the end of treatment: 9.55%, SD = 1.086 in the initial instance, and 7.77%, SD = 1.164 in the final instance.

Table 1. General profile of patients.

Age	Average 59.70 years, standard deviation (SD) of 9.073 years
Sex	Female: 6 (60.0%) Male: 4 (40.0%)
Weight (initial)	Average of 119.94 kg, SD = 13.86 kg.
Height	1.72 m, SD = 0.054 m.
Circumference	125.60 cm, SD = 13.867 cm.
BMI (initial)	40.60 kg/m^2, SD = 6.542 kg/m^2.

Table 2. Mean baseline glycated hemoglobin by treatment group.

Biochemical parameter	Group 3 months	Group 6 months	Group 12 months
HbA_{1c} (%)	9.55, SD = 0.629*	8.71, SD = 0.932*	8.70, SD = 1.556*

*Statistically significant difference ($p < 0.05$).

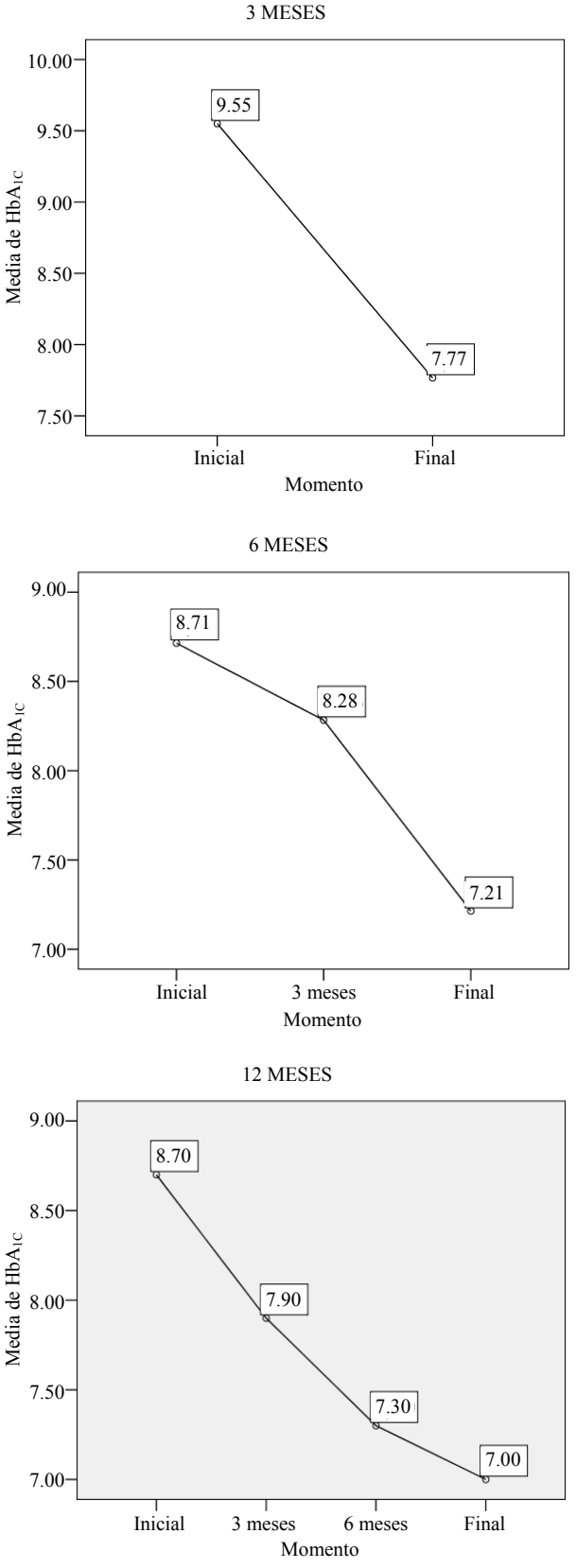

Figure 1. Graphs the means by treatment group and the corresponding cutoff.

In the group treated with Byetta® for 6 months, statistically significant differences ($p < 0.05$) in HbA_{1c} parameter ($F_{1.12} = 12.277$, $p = 0.004$), finding a significant decrease towards the end of treatment: 8.71%, SD = 0.932 in the initial instance, and 7.21, SD = 0.644 in the final instance.

Related to that, the statistically significant differences ($p < 0.05$) was found to consider jointly the initial request, 3 and 6 months ($F_{2.17} = 5.839$, $p = 0.012$). In this case, Duncan's test identified two homogeneous subgroups: early times and 3 months in one (mean 8.71% and 8.28%, respectively) and the other 6 months (mean 7.21%), thus indicating that a significant reduction occurs by 6 months of treatment.

Finally, regarding the group treated with Byetta® for 12 months, were found statistically significant differences ($p < 0.05$), corresponding to average values of 6.70%, SD = 1.556 in the initial instance, 7.90%, DT = 1.272 at 3 months, 7.30%, SD = 0.849 at 6 months and 6.70%, SD = 0.707 at 12 months.

At the end of treatment, we found similar effects of Byetta®, effects correlated with the decrease in HbA_{1c}. It is observed that HbA_{1c} is smaller (maximum reduction) in the group treated for 12 months (**Figure 1**).

4. Discussion

Significant effects of treatment with Byetta® in patients with type 2 diabetes mellitus were recorded for the parameter of HbA_{1c} from 3 to 6 months of administering the drug. Even in the latter case, the differences which were statistically significant ($p < 0.05$) were consistent with intermediate levels. Significant effects occurred for all patients indiscriminately about sex, age and initial BMI.

Despite this, and they were presented as baseline biochemical parameters inadequate, according to the criteria of optimal control of the SED [10,24], the final results of HbA_{1c} reached the limit of adequacy.

Exenatide was associated with a loss of weight compared to baseline values in **Table 2**. Exenatide appears to worsen the cardiovascular status of patients who specifically included in the study by having the risk of that disease.

Therefore, the recommendations of this study, in conclusion, result in the need for randomized studies to evaluate the effects of Byetta®, interpreted as sensitizers, on different physical and biochemical parameters in a greater long-term, proposing to do, at a minimum of 2 years.

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