

EXENATIDE AND LIRAGLUTIDE – SIDE EFFECTS. COMPARATIVE CLINICAL STUDY

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Abstract

The objective of this study was to monitor the side effects of two agonists of GLP-1 (glucagon-like peptide 1), exenatide and liraglutide, in order to determine their safety, tolerability and therapeutic efficiency. The study took place in the *Heart and Diabetes Center NRW*, Germany and overweight patients with type 2 diabetes whose therapeutic regimen was switched to incretin mimetics were included. A validated questionnaire method was used to monitor the side effects during the hospitalization period, then again at 3, respectively 6 months after the beginning of the treatment.

The therapy with liraglutide was associated with fewer side effects than the one with exenatide. In general, side effects were declining with time, thus, only few patients stopped the treatment. The incretin therapy turned out to be a safe and effective therapeutic option for patients with type 2 diabetes mellitus.

Rezumat

Obiectivul acestui studiu a fost monitorizarea efectelor secundare a doi agoniști de GLP-1 (*glucagon-like peptide 1*), exenatida și liraglutida, în scopul determinării profilului de siguranță, tolerabilitate și eficiență terapeutică a acestora. Studiul s-a desfășurat în *Herz und Diabetes Zentrum NRW*, Germania și a cuprins pacienți supraponderali cu diabet zaharat tip 2, a căror regim terapeutic a fost schimbat cu incretin mimetice. O metodă validă a chestionarelor a fost folosită pentru monitorizarea efectele secundare de-a lungul perioadei de spitalizare, iar apoi la 3, respectiv 6 luni de la inițierea terapiei. Terapia cu liraglutidă a fost asociată cu mai puține efecte secundare decât cea cu exenatidă. În general, efectele secundare au scăzut în timp, astfel că doar puțini pacienți au întrerupt terapia. Tratamentul incretinic s-a dovedit a fi o opțiune terapeutică sigură și eficientă pentru pacienții cu diabet zaharat tip 2.

Keywords: exenatide, liraglutide, side effects, glucagon-like peptide 1.

Introduction

Diabetes mellitus is the most frequent endocrine disease and, through its frequency, it enters the so-called category of chronic diseases of civilization. The treatment for type 2 diabetes mellitus (T2DM) implies a wide range of medications which differ in terms of mechanism of action,

pharmacology, way of administration, safety and clinical efficiency, tolerability, side effects, interactions, etc.

Nowadays, therapeutic regimes for the treatment of T2DM often include the endogen incretin glucagon-like peptide-1 (GLP-1) which together with glucose-dependent insulinotropic polypeptide (GIP), is released by the intestinal cells as a reaction to the oral administration of a nutrient, especially of glucose, and can determine insulin release in physiological concentrations, *in vivo* [1]. GLP-1 determines many other effects, such as postprandial decrease of glucagon secretion in pancreatic α -cells [2], increased pancreatic β -cell proliferation and neurogenesis [3], decreased β -cells apoptosis [4], stimulation of non-insulin-secreting pancreatic cells to produce insulin [5], lowering of gastric emptying, induction of gastric distention [6], increased satiety and reduced sense of appetite [7], etc. The average half-life of GLP-1 is approx. 2 minutes, as it is rapidly degraded by the enzyme dipeptidylpeptidase 4 (DPP-4) [8].

Exenatide is an analogue of GLP-1 and exerts the biological effects of the intestinal hormone. Due to its structure, exenatide is resistant to the action of DPP-4, having a half-life time of 10 hours [9]. Exenatide therapy involves subcutaneous injection twice daily [10]. The most frequent side effects of exenatide were recorded at gastrointestinal level [11].

Liraglutide is an agonist of GLP-1 with a prolonged half-life of 11-15 hours [12] and is administered subcutaneously every 24 hours [13]. The side effects are mainly of gastrointestinal nature [14].

Materials and Methods

Patients

The patients subjected to the evaluation on incretin mimetics were selected consecutively over an 11 months' period from the Heart and Diabetes Center NRW in Bad Oeynhausen, Germany. The ethics committee of the Ruhr University of Bochum located at the Heart and Diabetes Center NRW approved this data acquisition. All patients have never been treated with these substances before; therapy change was performed during hospital stay following clinical affordance. After informed consent patients were asked to take part in this data collection and were followed up for 6 months. The new therapy offered to them in the treatment of diabetes type 2 consisted in: exenatide, or liraglutide, respectively – which were administered as a therapy associated to other antidiabetic drugs (metformin, glimepiride, pioglitazone, etc.).

As these patients were selected consecutively and not to predetermined criteria this cohort presents a real life patients cohort. The

clinical parameters concerning side effects were: nausea, vomiting, heartburns (pyrosis), hiccups (eructation), diarrhea, constipation, headaches, and dizziness.

The overall profile of these side effects was based on the questionnaire method which followed three chronological points of reference in time: “point 0” – the hospitalization period (the beginning of the therapy), “point 1” – three months after the therapy started, “point 2” – six months after the therapy started. At “point 0” the records had in view the side effects’ incidence within every single day of the approximately 7-10 days of the hospitalization period. The questionnaires used at point 1 and 2 focused solely on recording the incidence of these adverse reactions within three consecutive days.

Before the monitoring of side effects, records had been made with data regarding the incidence of these reactions in the patients before the hospitalization period. In order to record all data as precisely as possible, the factors taken under consideration were extended to: the history of previous medication, the medication associated to the study therapy, and other factors like environment, temperature, diet etc. which could have influenced the patient’s condition.

Results and Discussion

The study included initially 210 patients with available data sets. Of those, 112 patients (mean age 58.4 ± 11.8 years) were treated with exenatide and 98 patients (mean age 57.9 ± 11.8 years) with liraglutide.

For the side effects monitoring, each occurrence of a side effect during the hospitalizing period was counted as ‘negative event’. Each improvement in relation to the patient’s condition before the therapy started was counted as ‘positive event’. In the results tables, the incidence of side effects occurrence is presented as follows: each side effect during hospitalization period was counted only once, regardless of its duration.

The table I shows that the incidence of side effects occurrence, except from pyrosis, is higher in the exenatide group. On the contrary, the incidence of ‘the positive events’ occurrence is higher in liraglutide group. The most frequent side effect turned out to be nausea (33.0% for exenatide and 25.5% for liraglutide) and eructation (27.7% for exenatide and 26.5% for liraglutide). The remarkable positive events were recorded in patients with intestinal transit disorders such as constipation (positive events: 11.6% - exenatide group and 15.3% - liraglutide group) or diarrhea (positive events: 8.9% - exenatide group and 16.3% - liraglutide group). Three months after the therapy started fewer side effects both in exenatide and

liraglutide groups, except for pyrosis, were described by the patients (table II). Six months after the therapy, the side effects incidence showed the lowest values recorded along the monitoring period (table III).

Table I
Incidence of side effects throughout the hospitalization period

	Exenatide Group 112 Patients		Liraglutide Group 98 Patients	
	–	+	–	+
Nausea	37 (33.0%)	1 (0.9%)	25 (25.5%)	9 (9.2%)
Vomiting	9 (8.0%)	–	3 (3.1%)	4 (4.1%)
Pyrosis	7 (6.3%)	3 (2.7%)	7 (7.1%)	10 (10.2%)
Eructation	31 (27.7%)	7 (6.3%)	26 (26.5%)	8 (8.2%)
Diarrhea	30 (26.8%)	10 (8.9%)	20 (20.4%)	16 (16.3%)
Constipation	21 (18.8%)	13 (11.6%)	18 (18.4%)	15 (15.3%)
Headaches	29 (25.9%)	2 (1.8%)	13 (13.3%)	9 (9.2%)
Dizziness	21 (18.8%)	4 (3.6%)	14 (14.3%)	9 (9.2%)

Table II
Incidence of side effects three months after the therapy start

	Exenatide group 92 Patients		Liraglutide Group 83 Patients	
	–	+	–	+
Nausea	19 (20.7%)	-	20 (24.1%)	4 (4.8%)
Vomiting	7 (7.6%)	-	2 (2.4%)	3 (3.6%)
Pyrosis	6 (6.5%)	3 (3.3%)	11 (13.3%)	8 (9.6%)
Eructation	25 (27.2%)	6 (6.5%)	14 (16.9%)	6 (7.2%)
Diarrhea	16 (17.4%)	8 (8.7%)	14 (16.9%)	12 (14.5%)
Constipation	14 (15.2%)	12 (13.0%)	11 (13.3%)	13 (15.7%)
Headaches	13 (14.1%)	1 (1.1%)	5 (6.0%)	6 (7.2%)
Dizziness	14 (15.2%)	3 (3.3%)	8 (9.6%)	5 (6.0%)

Table III
Incidence of side effects six months after the therapy start

	Exenatide Group 79 Patients		Liraglutide Group 76 Patients	
	–	+	–	+
Nausea	16 (20.3%)	-	5 (6.6%)	4 (5.3%)
Vomiting	4 (5.1%)	-	1 (1.3%)	2 (2.6%)
Pyrosis	2 (2.5%)	1 (1.3%)	4 (5.3%)	7 (9.2%)
Eructation	14 (17.7%)	5 (6.3%)	5 (6.6%)	5 (6.6%)
Diarrhea	10 (12.7%)	8 (10.1%)	8 (10.5%)	12 (15.8%)
Constipation	9 (11.4%)	11 (13.9%)	8 (10.5%)	12 (15.8%)
Headaches	10 (12.7%)	1 (1.3%)	-	5 (6.6%)
Dizziness	8 (10.1%)	2 (2.5%)	4 (5.3%)	4 (5.3%)

Considering both are agonists of GLP-1, the side effects, especially nausea, were more often reported among women. Symptoms of dizziness were more frequent among men when treated with liraglutide (table IV). Both therapies were associated with higher numbers of the adverse effects like pyrosis and eructation, which were more frequent in patients aged between 20 and 60 years than in patients aged 61 to 85 years. On the contrary, nausea, vomiting and dizziness had a higher frequency in the later age group (Table V). Table VI gives clear evidence to the fact that the incidence of most adverse reactions is increased when combining GLP-1 agonists with metformin rather than with sulfonylureas with exception of nausea and eructation in the liraglutide group, as well constipation and headaches in the exenatide group. Also worth mentioning is the fact that the recording of a small number of moderate hypoglycemic cases appeared in combination of GLP-1 agonists with sulfonylureas, which was known previously.

Table IV
The incidence of adverse effects according to gender
during the hospitalization period

	Exenatide Group				Liraglutide Group			
	112 Patients				98 Patients			
	45 women		67 men		36 women		62 men	
	-	+	-	+	-	+	-	+
Nausea	21 (46.7%)	1 (2.2%)	16 (23.9%)	-	13 (36.1%)	6 (16.7%)	12 (19.4%)	3 (4.8%)
Vomiting	4 (8.9%)	-	5 (7.5%)	-	1 (2.8%)	4 (11.1%)	2 (3.2%)	-
Pyrosis	4 (8.9%)	-	3 (4.5%)	3 (4.5%)	3 (8.3%)	5 (13.9%)	4 (6.5%)	5 (8.1%)
Eructation	17 (37.8%)	5 (11.1%)	14 (20.9%)	2 (3.0%)	13 (36.1%)	5 (13.9%)	13 (21.0%)	3 (4.8%)
Diarrhea	15 (33.3%)	3 (6.7%)	15 (22.4%)	7 (10.4%)	11 (30.6%)	6 (16.7%)	9 (14.5%)	10 (16.1%)
Constipation	10 (22.2%)	6 (13.3%)	11 (16.4%)	7 (10.4%)	8 (22.2%)	5 (13.9%)	10 (16.1%)	10 (16.1%)
Headaches	15 (33.3%)	2 (4.4%)	14 (20.9%)	-	6 (16.7%)	5 (13.9%)	7 (11.3%)	4 (6.5%)
Dizziness	9 (20.0%)	2 (4.4%)	12 (17.9%)	2 (3.0%)	4 (11.1%)	6 (16.7%)	10 (16.1%)	3 (4.8%)

Table V
The incidence of adverse effects depending on patient's age during the
hospitalization period

	Exenatide Group				Liraglutide Group			
	112 Patients				98 Patients			
	64 Patients (20-60 years)		48 Patients (61-85 years)		52 Patients (20-60 years)		46 Patients (61-85 years)	
	-	+	-	+	-	+	-	+
Nausea	20 (31.3%)	1 (1.6%)	17 (35.4%)	-	10 (19.2%)	3 (5.8%)	15 (32.6%)	6 (13.0%)
Vomiting	4 (6.3%)	-	5 (10.4%)	-	1 (1.9%)	2 (3.8%)	2 (4.3%)	2 (4.3%)
Pyrosis	4 (6.3%)	2 (3.1%)	3 (6.3%)	1 (2.1%)	5 (9.6%)	6 (11.5%)	2 (4.3%)	4 (8.7%)
Eructation	19 (29.7%)	4 (6.3%)	12 (25.0%)	3 (6.3%)	14 (26.9%)	3 (5.8%)	12 (26.1%)	5 (10.9%)
Diarrhea	16 (25.0%)	5 (7.8%)	14 (29.2%)	5 (10.4%)	12 (23.1%)	5 (9.6%)	8 (17.4%)	11 (23.9%)
Constipation	11 (17.2%)	4 (6.3%)	10 (20.8%)	9 (18.8%)	11 (21.2%)	8 (15.4%)	7 (15.2%)	7 (15.2%)
Headaches	16 (25.0%)	2 (3.1%)	13 (27.1%)	-	7 (13.5%)	6 (11.5%)	6 (13.0%)	3 (6.5%)
Dizziness	12 (18.8%)	1 (1.6%)	9 (18.8%)	3 (6.3%)	6 (11.5%)	3 (5.8%)	8 (17.4%)	6 (13.0%)

Table VI

The incidence of side effects in patients receiving concomitant therapy with metformin or sulfonylureas during the hospitalization period

	Exenatide Group				Liraglutide Group			
	112 Patients				98 Patients			
	50 Patients Metformin		13 Patients sulfonylurea		37 Patients metformin		11 Patients sulfonylurea	
	-	+	-	+	-	+	-	+
Nausea	20 (40.0%)	1 (2.0%)	2 (15.4%)	-	10 (27.0%)	4 (10.8%)	4 (36.4%)	1 (9.1%)
Vomiting	7 (14.0%)	-	-	-	1 (2.7%)	1 (2.7%)	-	1 (9.1%)
Pyrosis	2 (4.0%)	1 (2.0%)	-	-	2 (5.4%)	4 (10.8%)	-	-
Eructation	15 (30.0%)	2 (4.0%)	3 (23.1%)	-	8 (21.6%)	3 (8.1%)	5 (45.5%)	2 (18.2%)
Diarrhea	17 (34.0%)	5 (10.0%)	2 (15.4%)	-	9 (24.3%)	6 (16.2%)	1 (9.1%)	4 (36.4%)
Constipation	9 (18.0%)	4 (8.0%)	5 (38.5%)	3 (23.1%)	5 (13.5%)	5 (13.5%)	1 (9.1%)	-
Headaches	13 (26.0%)	-	4 (30.8%)	-	7 (18.9%)	4 (10.8%)	1 (9.1%)	2 (18.2%)
Dizziness	12 (24.0%)	2 (4.0%)	2 (15.4%)	-	4 (10.8%)	3 (8.1%)	1 (9.1%)	1 (9.1%)

During the 6 months monitoring, the therapy with exenatide was stopped in 19 of the 112 patients, because of the side effects, while only 4 of the 98 patients under liraglutide were subjected to treatment interruption. Only one patient under exenatide reported blurred vision and light nasal bleeding. Transient bloating and fullness were recorded under both therapies.

Conclusions

Regarding their incidence, the side effects monitored correspond to the data known in the literature, i.e. exenatide causes more side effects than liraglutide [15]. Also, the association of agonists of GLP-1 with metformin generates a higher number of adverse effects with exception of nausea, eructation, constipation and headaches. Side effects were generally quickly reversible; their incidence was declining during the monitoring period. Under these therapies, the data recorded an improvement in some of the patients with bowel transit problems. The new therapeutic concept of GLP-1 analogs is easily and successfully applied in overweight patients with type 2 diabetes mellitus.

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The first two authors have equal contribution to the study

References

1. Nielson LL, Young AA, Parkes DG. Pharmacology of exenatide (synthetic exendin-4): a potential therapeutic for improved glycemic control of type 2 diabetes. *Regul Pept.* 2004;117:77-88.
2. Orskov C, Holst JJ, Nielsen OV. Effect of truncated Glucagon-like peptide-1 [proglucagon-(78-107) amide] on endocrine secretion from pig pancreas, antrum, and nonantral stomach. *Endocrinology*, 1988;123:2009-2013.
3. Hols JJ. On the physiology of GIP and GLP-1. *Horm Metab Res.* 2004;36:747-754.
4. Nie Y, Nakashima M, Brubaker PL, et al. Regulation of pancreatic PC1 and PC2 associated with increased glucagon and GLP-1 immunoreactivity in diabetic rats. *J Clin Invest.* 2000;105:955-965.
5. Zhou J, Wang X, Pineyro MA, Egan JM. Glucagon-like peptide 1 and exendin-4 convert pancreatic AR42J cells into glucagon- and insulin-producing cells. *Diabetes*, 1999;48:2358-66.
6. Nauck MA, Niedereich-Holz U, Ettler R, et al. Glucagon-like peptide 1 inhibition of gastric emptying outweighs its insulinotropic effects in healthy humans, *J Physiol.* 1997;273:981-988.
7. Flint A, Raben A, Astrup A et al. Glucagon-like peptide 1 promotes satiety and suppresses energy intake in humans. *J Clin Invest.* 1998;101:515-520.
8. Barnett A. DPP-4 inhibitors and their potential role in the management of type 2 diabetes. *Int J Clin Pract.* 2006;60:1454-70.
9. Chen D, Lee SL, Peterfreund RA. New Therapeutic Agents for Diabetes Mellitus: Implications for Anesthetic Management. *A & A*, 2009;108:1803-1810.
10. Fineman MS, Bicsak TA, Shen LZ, et al. Effect on glycaemic control of exenatide (synthetic exendin-4) additive to existing metformin and/or sulfonylurea treatment in patients with type 2 diabetes. *Diabetes Care*, 2003;26:2370-7.
11. Rosenstock J, Klaff LJ, Schwartz S, et al. Effects of exenatide and lifestyle modification on body weight and glucose tolerance in obese subjects with and without pre-diabetes. *Diabetes Care*, 2010;33:1173-5.
12. Elbrond B, Jakobsen G, Larsen S, et al. Pharmacokinetics, pharmacodynamics, safety, and tolerability of a single-dose of NN2211, a long-acting glucagon-like peptide 1 derivative, in healthy male subjects. *Diabetes Care*, 2002;25:1398-404.
13. Juhl CB, Hollingdal M, Sturis J, et al. Bedtime administration of NN2211, a long-acting GLP-1 derivative, substantially reduces fasting and postprandial glycaemia in type 2 diabetes. *Diabetes*, 2002;51:424-9.
14. Chang AM, Jakobsen G, Sturis J, et al. The GLP-1 derivative NN2211 restores beta-cell sensitivity to glucose in type 2 diabetic patients after a single dose. *Diabetes*, 2003;52:1786-91.
15. Sten Madsbad. Exenatide and liraglutide: different approaches to develop GLP-1 receptor agonists (incretin mimetics) – preclinical and clinical results. *Best Practice & Research Clinical Endocrinology & Metabolism*, 2009;23:463-477.

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