doi: 10.1111/j.1463-1326.2008.00861.x

Patient-reported rating of gastrointestinal adverse effects during treatment of type 2 diabetes with the once-daily human GLP-1 analogue, liraglutide

Glucagon-like peptide-1 (GLP-1), an incretin hormone secreted in response to food intake [1], has been demonstrated to reduce appetite, food intake and body weight and to slow gastric emptying. Its biological effects include a glucose-dependent insulinotropic effect on the pancreatic cells. The main adverse effects (AEs), which are gastrointestinal (GI), appear to be dose related and may result from GLP-1's inhibition of gastric emptying.

Liraglutide is a human GLP-1 analogue designed for once-daily administration in patients with type 2 diabetes mellitus (T2DM). It lowers blood glucose by stimulating endogenous insulin secretion, decreasing blood glucagon levels and slowing gastric emptying. In a 14-week monotherapy study in T2DM patients, liraglutide significantly improved glycaemic control, lowered body weight and was associated with improvements in beta-cell function and cardiovascular biomarkers [2–4]. Liraglutide is generally well tolerated. As with native GLP-1, the main AEs occur within the GI system (diarrhoea, constipation and nausea) and appear to be generally mild–moderate and transient in nature [5,6]. The aim of this study was to evaluate GI AEs, for the first time, by using the Gastrointestinal System Rating Scale (GSRS) [7], a validated self-reporting instrument.

Subjects, Materials and Methods

The present study was part of a larger double-blind, placebo-controlled, randomized trial conducted over 14 weeks for which the primary objective was to assess and compare the efficacy of three doses of liraglutide vs. placebo on glycaemic control [2]. The study included T2DM patients, with body mass index $\leq$40 kg/m^2, 7.5% $\leq$ haemoglobin A_{1c} (HbA_{1c}) $\leq$ 10% (for previously diet treated), 7.0% $\leq$ HbA_{1c} $\leq$ 9.5% (for previously oral antidiabetic drug monotherapy treated), randomized to three doses of liraglutide (0.65, 1.25 or 1.90 mg/day) or to placebo. The trial was carried out in accordance with Good Clinical Practice guidelines and was approved by ethics committees and health authorities according to local regulations. Denmark, France, the Netherlands and Slovakia participated in the main study; Slovakia was not included in the GSRS substudy as a linguistically validated translation of the GSRS questionnaire was unavailable. The GSRS was completed at randomization (baseline) and after 2, 4, 8 and 14 weeks of treatment. The validated GSRS [8] included 15 items on five dimensions (diarrhoea, indigestion, constipation, abdominal pain and reflux), each graded on a seven-point Likert scale from no (score 1) to very severe (score 7) discomfort. Scores were calculated as the mean value of each item in the five dimensions. Scores from each liraglutide-treated group were compared with the placebo group using Fisher's exact test by categorizing patients with an increase or no increase/decrease in GSRS rating.

Results

Baseline Characteristics of Patients

Results of the main study have been published [2]. The baseline characteristics of all four groups were well matched; for the subgroup of patients (n = 81) completing the GSRS questionnaire, these were comparable with the whole trial population, although the male : female ratio was higher in the liraglutide groups compared with the placebo group (table 1).

Patient-completed GSRS

All treatment groups had low average GSRS ratings at randomization (placebo 1.3–1.6 and liraglutide 1.1–1.7 on a seven-point Likert scale) and at end of the trial (placebo 1.0–1.2 and liraglutide 1.1–1.6). Differences in GSRS ratings between liraglutide and placebo groups were predominantly seen within 2 weeks of treatment initiation (placebo 1.0–1.6 and liraglutide 1.4–2.0); thereafter, GSRS ratings decreased towards baseline levels (figure 1a–e).

Correspondence:
Michael Horowitz, Department of Medicine, Level 6, Eleanor Harrald Building, Royal Adelaide Hospital, North Terrace, Adelaide, South Australia 5000, Australia.
E-mail:
michael.horowitz@adelaide.edu.au

Table 1 Baseline characteristics

Baseline characteristics	0.65 mg liraglutide	1.25 mg liraglutide	1.90 mg liraglutide	Placebo
Exposed (n)	21	21	19	20
Completers (n)	18	19	15	12
Sex (male : female) (%)	15 : 6	16 : 5	16 : 3	9 : 11
Age (years)	60 (10)	54 (11)	59 (12)	59 (11)
Duration of diabetes (years)	7 (1–25)	7 (0–21)	4 (1–10)	4 (1–12)
Previous treatment (diet : monotherapy OAD%)	29 : 71	24 : 76	11 : 89	15 : 85
HbA_{1c} (%)	7.7 (0.7)	8.1 (0.6)	7.8 (0.5)	7.7 (0.5)
BMI (kg/m^2)	28.9 (4.3)	30.8 (5.0)	29.3 (4.6)	30.1 (4.3)

BMI, body mass index; HbA_{1c}, haemoglobin A_{1c}; OAD, oral antidiabetic drug.
Age, sex [means (s.d.)], duration of diabetes [median (range)] and previous treatment were recorded at screening and diabetes characteristics [means (s.d.)] at baseline.

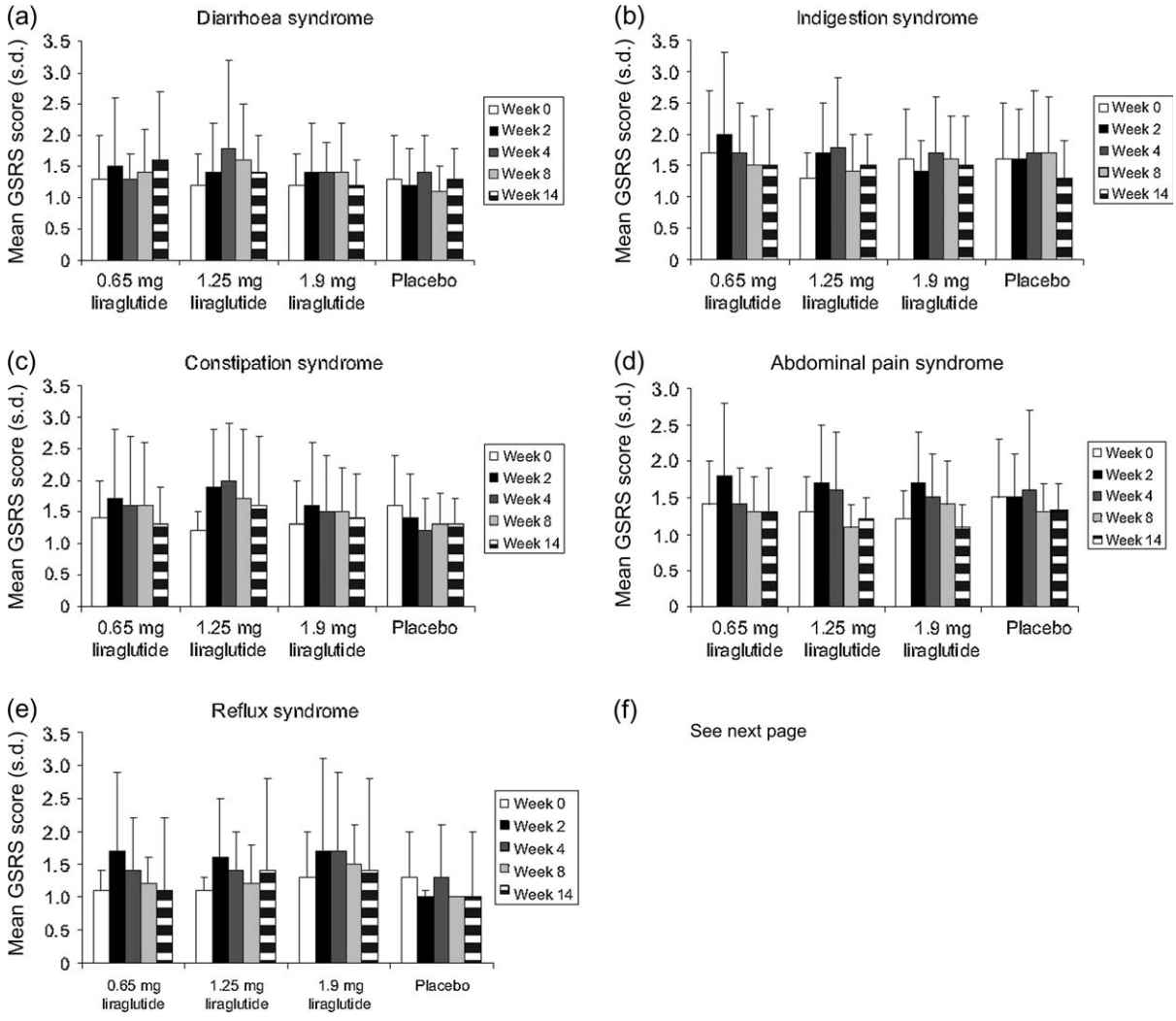

Fig. 1 Gastrointestinal adverse effects evaluated by the Gastrointestinal System Rating Scale (GSRS) by patients with type 2 diabetes mellitus treated with liraglutide or placebo for 14 weeks. (a–e) Graphic presentation of mean GSRS score (s.d.) by treatment and GSRS dimension. (f) Comparison of increase and decrease/no change in GSRS rating as measured by the GSRS for liraglutide vs. placebo treatment.

(f)

	Diarrhoea			Indigestion			Constipation			Abdominal Pain			Reflux		
	I*	D/ NC†	p#	I*	D/ NC†	p#	I*	D/ NC†	p#	I*	D/ NC†	p#	I*	D/ NC†	p#
0.65 mg liraglutide	4	15	1.0000	6	13	0.0918	6	13	0.0918	6	13	0.0918	4	15	0.1062
1.25 mg liraglutide	7	13	0.2876	8	12	0.0227	8	12	0.0227	5	15	0.1886	5	15	0.0498
1.90 mg liraglutide	5	15	0.7013	5	15	0.1886	6	14	0.0975	3	17	0.6088	7	13	0.0094
Placebo	3	14	-	1	16	-	1	16		1	16		0	17	

*Number of patients experiencing an increase (I) in GSRS score from baseline to 14 weeks of treatment.

†Number of patients experiencing a decrease (D) or no change (NC) in GSRS score from baseline to 14 weeks of treatment.

#p value estimated by Fisher's exact test for difference compared with placebo-treated patients.

Fig. 1 Continued.

While there was a tendency towards more subjects reporting an increase in symptoms after liraglutide compared with placebo treatment, only the reflux GSRS rating showed a significant, dose-dependent response ($p < 0.05$ for 1.25 mg and 1.90 mg). For indigestion and constipation, only the 1.25 mg dose reached statistical significance (both $p < 0.05$), and for diarrhoea and abdominal pain, there were no statistical differences between placebo and liraglutide at any dose (figure 1f).

Discussion

GLP-1 analogues are known to be associated with GI AEs; AE rate and severity are linked to treatment adherence. In the current study, the GSRS was used to quantify the duration and intensity of GI AEs from the patient's perspective during 14 weeks of liraglutide treatment. While liraglutide treatment increased GI symptoms, with a significant effect on the reflux, indigestion and constipation dimensions, the average GSRS ratings remained low for all treatment groups (maximum 2 on a seven-point scale). The reported increase in GI AEs was mainly observed during the first 2 weeks of treatment; thereafter, symptoms returned towards baseline scores, supporting previous evidence that liraglutide GI AEs are usually mild and transient in nature [5,6]. It should be recognized, however, that this was not predictable: in traditional assessment of AEs, patients may be reluctant to give information on GI or other symptoms, leading to underestimation of prevalence and severity. Furthermore, patients with diabetes rarely volunteer information spontaneously about GI symptoms. The use of the self-administered GSRS questionnaire, formally quantifying by use of a validated measure, adds important and novel complementary information to the efficacy and safety variables traditionally evaluated in clinical studies.

M. Horowitz
Department of Medicine, North Terrace, Royal Adelaide Hospital, Adelaide, Australia
T. Vilsbøll
Department of Internal Medicine F, Gentofte Hospital, Copenhagen, Denmark
M. Zdravkovic, M. Hammer
Novo Nordisk A/S, Bagsværd, Denmark
S. Madsbad
Department of Endocrinology, Hvidovre University Hospital, University of Copenhagen, Hvidovre, Denmark

Acknowledgement

This study was sponsored by Novo Nordisk.

References

1 Ørskov C. Glucagon-like peptide-1, a new hormone of the entero-insular axis. Diabetologia 1992; **35:** 701–711.
2 Vilsbøll T, Zdravkovic M, Le Thi T *et al.* Liraglutide, a long-acting human glucagon-like peptide-1 analog, given as monotherapy significantly improves glycemic control and lowers body weight without risk of hypoglycemia in

patients with type 2 diabetes. Diabetes Care 2007; **30:** 1608–1610.

3 Vilsboll T, Zdravkovic M, Le-Thi T *et al.* Liraglutide treatment, blood pressure and biomarkers of cardiovascular risk in patients with type 2 diabetes: 14 weeks monotherapy study. Diabetes 2006; **55** (Suppl. 1)**:** A465.

4 Vilsbøll T, Brock B, Perrild H *et al.* Liraglutide, a once-daily human GLP-1 analogue improves beta-cell function and arginine-stimulated insulin secretion at hyperglycaemia in patients with type 2 diabetes mellitus. Diabet Med 2007: DOI: 10.111/j.1464-5491.2007.02333.x

5 Madsbad S, Schmitz O, Ranstam J, Matthews DR. Improved glycemic control with no weight increase in patients with type 2 diabetes after once-daily treatment with the long-acting glucagon-like peptide 1 analog liraglutide (NN2211): a 12-week, double-blind, randomized, controlled trial. Diabetes Care 2004; **27:** 1335–1342.

6 Nauck MA, Hompesch M, Filipczak R, Le TD, Zdravkovic M, Gumprecht J. NN2211-1499 study group. Five weeks of treatment with the GLP-1 analogue liraglutide improves glycaemic control and lowers body weight in subjects with type 2 diabetes. Exp Clin Endocrinol Diabetes 2006; **114:** 417–423.

7 Dimenas E, Glise H, Hallerbäck B, Hernqvist H, Svedlund J, Wiklund I. Quality of life in patients with upper gastrointestinal symptoms. An improved evaluation of treatment regimens? Scand J Gastroenterol 1993; **28:** 681–687.

8 Dimenas E, Glise H, Hallerbäck B, Hernqvist H, Svedlund J, Wiklund I. Well-being and gastrointestinal symptoms among patients referred to endoscopy owing to suspected duodenal ulcer. Scand J Gastroenterol 1995; **30:** 1046–1052.