

Liraglutide, a long-acting human GLP-1 Analog, given as Monotherapy Significantly Improves Glycemic Control and Lowers Body Weight without Risk of Hypoglycemia in Patients with Type 2 Diabetes Mellitus

Running title: Effect of liraglutide on glycemic control and weight

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Liraglutide is a long-acting human GLP-1 analog(1-4) and the current study was undertaken in order to evaluate efficacy and safety after 14 weeks treatment with liraglutide in patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS

Main inclusion criteria were patients aged ≥ 18 years with type 2 diabetes and $7.5\% \leq \text{HbA}_{1c} \leq 10.0\%$ (diet) or $7.0\% \leq \text{HbA}_{1c} \leq 9.5\%$ (mono-OAD) (previous therapy was discontinued). Fasting plasma glucose (FPG) at randomization was 7-13 mmol/l. If FPG > 15 mmol/l during the study the patient was withdrawn. The study was conducted in accordance with the Declaration of Helsinki(5). The study was double-blind, randomized (1:1:1:1), placebo-controlled using three doses of liraglutide (0.65, 1.25 or 1.90 mg). The following main efficacy parameters were assessed: HbA_{1c} , insulin, pro-insulin, glucagon, fructosamine, lipids, home-measured 7-point PG profiles and body weight. Safety parameters (adverse events (AE), hypoglycemic episodes, clinical laboratory parameters, antibodies against liraglutide, vital signs, ECG, thyroid (incl. ultrasonography) and parathyroid parameters) were assessed. Liraglutide or placebo was administered in the evening (as in the most recently completed phase 2 study (6)) as once daily sc. injections in the abdomen or thigh.

RESULTS

Baseline characteristics are given in Table 1. The placebo group accounted for almost half of the patient withdrawals, primarily due to ineffective therapy. Withdrawals due to AE were infrequent and occurred at a comparable level in all groups (Table 1).

After 14 weeks of treatment estimated change in HbA_{1c} for placebo, 1.90, 1.25 or 0.65 mg was +0.29, -1.45, -1.40, -0.98%, respectively (change for 1.90 mg vs. placebo: -1.74% [95% CI, -2.18; -1.29] $P < .0001$, 1.25 mg vs. placebo: -1.69% [-2.13; -1.24] $P < .0001$, 0.65 mg vs. placebo: -1.27% [-1.72; -0.82] $P < .0001$). The proportion of patients reaching $\text{HbA}_{1c} < 7\%$ was 46% (1.90 mg), 48% (1.25 mg), 38% (0.65 mg), and 5% (placebo) in the four groups. FPG

was significantly reduced (1.90 mg vs. placebo: -3.4 mmol/l [-4.4; -2.4] $P < .0001$, 1.25 mg vs. placebo: -3.4 mmol/l [-4.4; -2.4] $P < .0001$, 0.65 mg vs. placebo: -2.7 mmol/l [-3.7; -1.7] $P < .0001$). For the 1.90 group dose groups the fraction of patients reaching 90 min post meal glucose values below the ADA treatment goal of < 10 mmol/l was 46%, 51% and 56% of patients after breakfast, lunch and dinner, respectively. Corresponding values were 15%, 23%, and 23%, respectively, in the placebo treated group. For both the 1.90 and 1.25 mg dose groups the fraction of patients with $\text{PG} < 10$ mmol/l was significantly different from placebo ($p < 0.05$) at each meal, respectively. Analysis of HOMA showed a significant increase; 1.90 mg vs. placebo: 86% [48%; 134%] $P < .0001$, 1.25 mg vs. placebo: 134% [86%; 193%] $P < .0001$, 0.65 mg vs. placebo: 75% [40%; 120%] $P < .0001$. A dose dependent decrease in insulin resistance (HOMA) was observed (NS). The median change from baseline in pro-insulin/insulin ratio was significant for all three liraglutide groups vs. placebo: 1.90 mg -0.19, $P = 0.0111$; 1.25 mg -0.28, $P = 0.0062$; 0.65 mg -0.15, $P = 0.0218$.

Body weight decreased in all treatment groups with a maximum estimated loss of 2.99 kg in the 1.90 mg liraglutide group. The difference to placebo was significant for the 1.90 mg group (-1.21 kg [-2.36; -0.06] $P = 0.0390$). There was a significant lowering in fasting glucagon concentrations in the 1.90 mg liraglutide group compared with placebo (-3.26 pmol/l [-6.52; -0.00] $P = 0.0497$). Systolic blood pressure (BP) decreased significantly (1.90 mg vs. placebo: -7.9 mmHg [-12.9; -2.9] $P = 0.0023$, 1.25 mg vs. placebo: -5.2 mmHg [-10.2; -0.2] $P = 0.0417$, 0.65 mg vs. placebo: -7.4 mmHg [-12.4; -2.4] $P = 0.0041$). Diastolic BP dropped 2-3 mmHg using all doses of liraglutide when compared to placebo (NS). There was no significant effect on pulse, or clinically relevant changes in ECG. Lipid parameters (TC, LDL-C, VLDL-C, HDL-C, FFA and apoB) showed no consistent changes among treatment. Triglyceride levels decreased compared with placebo (1.90 mg vs. placebo: -22% [-35%; -6%] $P = 0.0110$, 1.25 mg

vs. placebo: -15%[-30%;2%] $P=0.0854$, 0.65 mg vs. placebo: -19%[-33%;-2%] $P=0.0304$).

The overall fraction of patients with adverse events (AEs) was comparable across the four groups, ranging from 43 to 51% of patients. The fraction of patients reporting a gastrointestinal (GI) AE was 37, 29, 38 and 23% of patients for 1.90 mg, 1.25 mg, 0.65 mg and placebo, respectively (NS), with a higher event rate reported at the highest dose group in comparison to placebo ($p<0.05$). The individual GI AEs were reported at similar frequencies across the liraglutide treatment groups although nausea seemed somewhat higher in the 1.90 and 0.65 mg groups (10% of subjects vs. 2-3% in the 1.25 mg and placebo groups). Diarrhea was reported by 26/123 and 5/40, nausea by 9/123 and 1/40 and vomiting by 4/123 and 0/40 subjects treated with liraglutide and placebo, respectively. Only 4/123 liraglutide treated patients withdrew from the study due to GI AEs. The incidence of GI AEs decreased over time. The effect on body weight did not change when excluding patients with duration of GI events >7 days. Three serious AEs were reported by 2 patients (one in the placebo group and one in the 1.90 mg group (influenza)). No major or minor hypoglycemic episodes were reported. There was no treatment related effect on induction of antibodies and no clinically relevant changes in safety laboratory parameters including thyroid ultrasonography were observed after treatment with liraglutide.

CONCLUSIONS

The present study demonstrated sustained effect of the long acting GLP-1 analog liraglutide on glycemic control in patients with type 2 diabetes without any major or minor hypoglycemic episodes. At the highest dose, liraglutide monotherapy reduced the estimated average HbA_{1c} levels by 1.74% from an

average HbA_{1c} of 8.5%, when compared to placebo. When given one of the two highest doses of liraglutide, almost half of the patients managed to reach the ADA target for postprandial control(7), confirming a full 24-hour coverage of liraglutide on glycemic control(8) Furthermore, in spite of improved glycemic control, which is often associated with an increase in body weight(9), a dose-dependent decrease in body weight was seen. Adverse events related to the gastrointestinal system and headaches were the most frequently reported adverse events. In addition to a beneficial effect of liraglutide on beta-cell function (current and in previous studies(10-12)), a potential effect on lowering of BP was observed in the current study. The mechanism behind the effect on BP remains unknown. However, since the effect on BP occurred earlier than the effect on body-weight, it suggests that the effect cannot only be ascribed to lowering in body-weight. In conclusion, the long-acting, once-daily GLP-1 analog, liraglutide, targets well-described abnormalities in the type 2 diabetic phenotype.

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Reference List

1. Agerso H, Vicini P: Pharmacodynamics of NN2211, a novel long acting GLP-1 derivative. *Eur J Pharm Sci* 19:141-150, 2003
2. Degn KB, Juhl CB, Sturis J, Jakobsen G, Brock B, Chandramouli V, Rungby J, Landau BR, Schmitz O: One week's treatment with the long-acting glucagon-like peptide 1 derivative liraglutide (NN2211) markedly improves 24-h glycemia and alpha- and beta-cell function and reduces endogenous glucose release in patients with type 2 diabetes. *Diabetes* 53:1187-1194, 2004
3. Knudsen LB, Nielsen PF, Huusfeldt PO, Johansen NL, Madsen K, Pedersen FZ, Thogersen H, Wilken M, Agerso H: Potent derivatives of glucagon-like peptide-1 with pharmacokinetic properties suitable for once daily administration. *J Med Chem* 43:1664-1669, 2000
4. Madsbad S, Schmitz O, Ranstam J, Jakobsen G, 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* 27:1335-1342, 2004
5. World Medical Association declaration of Helsinki. Recommendations guiding physicians in biomedical research involving human subjects. *JAMA* 277:925-926, 1997
6. Nauck MA, Hompesch M, Filipczak R, Le TD, Zdravkovic M, Gumprecht J: 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* 114:417-423, 2006
7. Standards of medical care in diabetes--2006. *Diabetes Care* 29 Suppl 1:S4-42, 2006
8. Degn KB, Juhl CB, Sturis J, Jakobsen G, Brock B, Chandramouli V, Rungby J, Landau BR, Schmitz O: One week's treatment with the long-acting glucagon-like peptide 1 derivative liraglutide (NN2211) markedly improves 24-h glycemia and alpha- and beta-cell function and reduces endogenous glucose release in patients with type 2 diabetes. *Diabetes* 53:1187-1194, 2004
9. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. *Lancet* 352:837-853, 1998
10. Piper K, Dijkstra I, Dunleavey L, Hanley NA: The Long-Acting GLP-1 Analog, Liraglutide, Increases Beta Cell Numbers during Early Human Development (Abstract). *Diabetologia* 2005
11. Rolin B, Larsen MO, Gotfredsen CF, Deacon CF, Carr RD, Wilken M, Knudsen LB: The long-acting GLP-1 derivative NN2211 ameliorates glycemia and increases beta-cell mass in diabetic mice. *Am J Physiol Endocrinol Metab* 283:E745-E752, 2002
12. Sturis J, Gotfredsen CF, Romer J, Rolin B, Ribel U, Brand CL, Wilken M, Wassermann K, Deacon CF, Carr RD, Knudsen LB: GLP-1 derivative liraglutide in rats with beta-cell deficiencies: influence of metabolic state on beta-cell mass dynamics. *Br J Pharmacol* 140:123-132, 2003

Table 1 Patient disposition and characteristics

	All	Liraglutide			Placebo
		1.90 mg	1.25 mg	0.65 mg	
Patient Disposition					
Screened	377				
Randomized	165				
Exposed	163	41	42	40	40
Withdrawn	25	6	3	5	11
adverse event	7	2	1	1	3
non-compliance	2	1	0	0	1
ineffective therapy	14	2	2	3	7
other	2	1	0	1	0
Completed	140	37	39	35	29
Included in ITT population	163	41	42	40	40
Baseline Characteristics					
Age (years)		55.4 (11.4)	53.8 (10.7)	56.5 (9.3)	57.7 (8.2)
Sex (Male/Female) (N)		30/11	23/19	27/13	19/21
BMI (kg/m ²)		29.9 (4.2)	31.2 (4.7)	28.9 (3.9)	30.4 (4.0)
HbA _{1c} (%)		8.5 (0.9)	8.3 (0.8)	8.1 (0.6)	8.2 (0.7)
Duration of diabetes (years)		4.0 (1 – 29)	7.0 (0 – 21)	6.0 (1 – 25)	5.0 (1 – 23)
Previous diabetes treatment					
diet		7	8	9	7
OAD (metformin)		14	19	15	17
OAD (SU)		19	14	16	15
OAD (repaglinide)		1	1	0	1
FPG (mmol/l)		12.3 (3.1)	11.9 (2.4)	11.3 (2.7)	11.3 (2.2)
Insulin (pmol/L)		63 (35)	60 (37)	59 (45)	70 (51)
Pro-insulin (pmol/L)		45 (28)	38 (19)	34 (24)	35 (20)
Pro-insulin to insulin ratio		0.74 (0.26)	0.70 (0.30)	0.88 (0.52)	0.59 (0.33)
Glucagon (pmol/L)		23 (7)	21 (7)	23 (9)	19 (6)
C-peptide (pmol/L)		1138 (455)	1076 (405)	1176 (640)	1260 (515)
Fructosamine (µmol/L)		360 (75)	341 (74)	358 (75)	330 (59)

Age, sex (means (SD)), duration of diabetes (median (range)) and previous treatment were recorded at screening and diabetes characteristics (means (SD)) at baseline. Two patients withdrew from the study before receiving study medication; one due to withdrawal of consent and one due to non-compliance.

The adverse event withdrawals were as follows: placebo – blood glucose increased (2 patients), hyperglycemia/nausea; 0.65 mg – diarrhea; 1.25 mg – injection site rash; 1.90 mg – tachypnoea/gastroesophageal reflux disease, constipation.