Competing interests

Nothing to declare.

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DOI: 10.1111/j.1464-5491.2008.02484.x

Beneficial effects of once-daily liraglutide, a human glucagon-like peptide-1 analogue, on cardiovascular risk biomarkers in patients with Type 2 diabetes

Liraglutide is a once-daily, human glucagon-like peptide-1 (GLP-1) analogue. Clinical studies have demonstrated blood glucose and weight-reducing effects, improvements in pancreatic B-cell function and a low risk of hypoglycaemic events with liraglutide [1,2]. Type 2 diabetes is associated with an increased risk of cardiovascular events. Recently, studies in patients with Type 2 diabetes have shown that native GLP-1 may also have beneficial effects on the myocardium [3] and on endothelial function [4].

We present here the effect of liraglutide on biomarkers for cardiovascular risk in patients with Type 2 diabetes, as an exploratory endpoint from a broader clinical study. The design and non-cardiovascular biomarker results of this study have been described previously [1]. The trial was carried out in accordance with good clinical practice. Briefly, 165 patients with Type 2 diabetes were randomized to either placebo or 0.65 mg, 1.25 mg or 1.9 mg liraglutide for 14 weeks. Across the four treatment arms, 17–23% of the subjects were previously treated with diet and exercise and the remaining subjects with oral glucose-lowering agents. Subjects had a mean body mass index (BMI) of 28.9–31.2 kg/m^2 and mean glycated haemoglobin (HbA_{1c}) at randomization of 8.1–8.5%. The study was powered against the primary endpoint HbA_{1c}, but was not powered at an 80% level for a difference of 20% for the cardiovascular biomarkers discussed here. At randomization and end of study, the following additional parameters were assessed: adiponectin, leptin, high-sensitivity C-reactive protein (hs-CRP), interleukin 6 (IL-6), tumour necrosis factor alpha (TNF-α), plasminogen activator inhibitor 1 (PAI-1) and B-type natriuretic peptide (BNP).

The data are presented in Table 1. A significant decrease in PAI-1 and BNP levels were observed following treatment with liraglutide. There was a non-significant, but dose-dependent, reduction in hs-CRP levels. There were no treatment effects on levels of adiponectin, leptin, IL-6 and TNF-α with liraglutide.

This study was part of a larger clinical trial, which showed significantly improved glycaemic control and a reduction in body weight in subjects treated with liraglutide [1]. In addition, systolic blood pressure (reduction of 8 mmHg at 1.90 mg/day vs. placebo) and plasma triglycerides (reduction of 22% at 1.90 mg/day vs. placebo) were significantly reduced [1]. PAI-1 and hs-CRP are inflammatory biomarkers that are associated with an increased risk of cardiovascular disease [5]. Elevated PAI-1 levels may suppress the fibrinolytic process and thereby be associated with the development of atherosclerosis. BNP is a marker of left ventricular dysfunction and elevated levels are risk markers for cardiovascular diseases, in particular for heart failure [6]. The findings suggest that liraglutide, when used to regulate blood glucose levels in patients with Type 2 diabetes, improves certain biomarkers associated with increased cardiovascular risk. Large prospective trials are needed to confirm these results and to assess whether these effects translate into improvements in cardiovascular risk in patients with Type 2 diabetes.

Competing interests

MZ and TL-T are employed by and hold stocks in Novo Nordisk A/S. TK is a member of advisory boards for Eli Lilly and Merck. TV has been reimbursed by Novo Nordisk and MSD for attending symposia, and for speaking, and is a member

Table 1 Baseline levels and change from baseline level of cardiovascular risk markers after 14 weeks of treatment

	Baseline level—mean (SD)* Liraglutide vs. placebo estimates (95% CI)† *P*-value‡			
Cardiovascular biomarker	Placebo	0.65 mg	1.25 mg	1.90 mg
PAI-1 (U/ml)	28.2 ± 20.0	27.8 ± 32.4 −14% (−35%; 14%) 0.29	22.0 ± 13.0 −29% (−47%; −6%) 0.018§	31.4 ± 28.4 −25% (−43%; −1%) 0.045§
BNP (ng/l)	42.8 ± 42.7	35.1 ± 22.9 −26% (−48%; 6%) 0.099	45.0 ± 38.4 −30% (−52%; −0%) 0.048§	40.6 ± 38.6 −38% (−57%; −12%) 0.0085§
Adiponectin (ng/ml)	4964 ± (3877)	4895 ± 2504 6% (−7%; 20%) 0.37	5713 ± 3415 6% (−7%; 20%) 0.39	3872 ± 2210 3% (−10%; 17%) 0.67
Leptin (pg/ml)	16 242 ± (12 717)	11 815 ± 11 991 14% (−2%; 32%) 0.085	13 724 ± 9105.8 26% (9%; 46%) 0.0017§	10 812 ± 9249.7 9% (−6%; 26%) 0.27
hs-CRP (mg/l)	4.3 ± (4.0)	3.1 ± 2.1 −3% (−32%; 38%) 0.85	3.9 ± 3.3 −12% (−38%; 25%) 0.46	4.2 ± 4.2 −20% (−44%; 14%) 0.22
IL-6 (pg/ml)	3.6 ± (3.9)	2.5 ± 1.7 −3% (−25%; 26%) 0.83	10.6 ± 52.4 4% (−20%; 34%) 0.79	2.8 ± 1.7 −2% (−25%; 27%) 0.87
TNF-α (pg/ml)	2.3 ± (1.5)	2.4 ± 1.5 −6% (−19%; 8%) 0.37	2.0 ± 0.9 1% (−12%; 16%) 0.90	2.4 ± 2.3 −4% (−17%; 11%) 0.58

*Mean ± SD of baseline values.
†Difference from placebo in change from baseline level in per cent, with 95% confidence interval.
‡*P*-value for change.
The cardiovascular risk biomarker parameters have been log transformed before applying the statistical model. Estimates are presented as per cent change. The estimates are obtained from an ANOVA with treatment and previous treatment as fixed effect and baseline value as covariate.
§Statistical significance at the 5% significance level.
BNP, B-type natriuretic peptide; CI, confidence interval; hs-CRP, high-sensitivity C-reactive protein; IL-6, interleukin 6; PAI-1, plasminogen activator inhibitor 1; SD, standard deviation; TNF-α, tumour necrosis factor alpha.

of advisory boards for MSD and Novartis. SM has served as a consultant or advisor to: Novartis Pharmaceuticals, Novo Nordisk, Merck-Sharp and Dome, Pfizer A/S, Abbott Laboratories, Sanofi-Aventis, Astra-Zeneca and Johnson & Johnson.

Acknowledgements

This trial was sponsored by Novo Nordisk A/S, Denmark. We would like to thank the following investigators and their staff. Denmark: K. Kølendorf, H. Perrild, S. Madsbad, T. Krarup, O. Schmitz, H. H. Lervang; France: J. P. Courreges, E. Aboud, C. Le Devehat, M. Vimeaux, D. Gouet, T. Godeau, M. v. Bernardin, M. Issa-Sayegh, Y. Hadjali, A. Blaimont, R. Mira, F. Galtier, A. Farret, J. P. Gagnol, Y. Lorcy, M. Rodier, A. Maubon, S. Schuldiner, B. Vialettes, C. Mattei, B. Catargi, B. Gatta, P. Duvezin-Caubat, P. Serusiat; Slovakia: Z. Nemethyova, T. Kupcova, M. Macko, I. Tkac, K. Suschozova, I. Buganova, L. Fabryova, V. Uliciansky, K. Raslova, P. Farkas, J. Okapcova, J. Fabry; the Netherlands: J. B. L. Hoekstra, P. H. L. M. Geelhoed-Duvestijn, P. A. Van Meurs, R. P. Verhoeven, H. Seinen, F. H. Kauw. We thank Ann Olling MSc for assistance in preparation of this manuscript.

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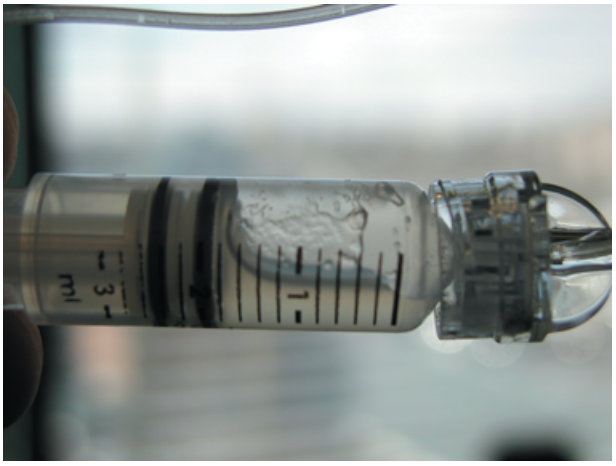

FIGURE 1 Gelled insulin within the insulin reservoir.

DOI: 10.1111/j.1464-5491.2008.02547.x

Gelling of insulin within an insulin pump reservoir

Herein I report a unique case of gelled solidification of insulin within an insulin reservoir and tubing in a patient with Type 1 diabetes treated with continuous subcutaneous insulin infusion (CSII) therapy.

A 29-year-old pregnant woman with a 21 year history of Type 1 diabetes, maintaining excellent blood glucose [blood glucose levels 4.0–7.5 mmol/l; glycated haemoglobin (HbA_{1c}) 6.0%] with CSII therapy using insulin lispro administered by a Medtronic Paradigm 712 pump (using a Quick-Set infusion set Medtronic Diabetes, Northridge, CA, USA), experienced sudden deterioration in blood glucose control with readings climbing to the high teens over a few hours. Corrective boluses of insulin were administered without improvement, at which point the patient inspected her insulin reservoir and observed the insulin to have gelled (Fig. 1). She reverted to conventional insulin injection and euglycaemia was restored quickly. Inspection of the vial itself revealed that it, unlike the reservoir, was free of solidification.

The patient subsequently obtained a new lot of insulin and, after several weeks of uneventful use, experienced the same phenomenon. She then switched to yet another insulin lot and no further problems were encountered.

Although crystallization of insulin administered by CSII has been identified previously [1,2], gelling of insulin within an insulin pump reservoir has not, as far as I am aware, been previously reported. Eli Lilly (pers. comm.), the manufacturer of the insulin in question, has advised me that insulin lispro can gel within a vial if the insulin is exposed to excess heat, overly vigorous shaking or if syringes and needles to withdraw the insulin are reused. The patient described herein had not exposed her insulin vial (or reservoir or pump) to excess heat, cold or humidity, had not subjected it to shaking, had not reused her syringes or needles and had not reused her insulin reservoir.

Analysis of the insulin vial by Eli Lilly revealed the presence of silicon (pers. comm.) thought to be related to piercing of the rubber stopper by the needle when drawing up insulin. Analysis of the contents of the gelled substance was requested, but not performed.

The aetiology of the gelling of the insulin is not known. However, as this hitherto unreported gelling of insulin within an insulin pump reservoir occurred twice in the same patient and with two different insulin lots, some patient-specific factor cannot be excluded. Regardless, individuals using CSII therapy and those assisting with their healthcare management will need to consider insulin gelling when determining the cause of sudden deterioration in blood glucose control.

Competing interests

I have received speaking honoraria from Eli Lilly, Novo Nordisk, Sanofi-Aventis and Medtronic Corporations.

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