

Efficacy of a continuous GLP-1 infusion compared to a structured insulin infusion protocol to reach normoglycemia in non-fasted type 2 diabetic patients – A clinical pilot trial

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Objective: Continuously administered insulin is limited by the need for frequent blood glucose measurements, dose adaption and risk of hypoglycemia. Alternatively, GLP-1-based regimens could represent a less complicated treatment alternative. This might be advantageous in hyperglycemic patients hospitalized for acute critical illness that profit from near normoglycemic control.

Research Design and Methods: In a prospective, open, randomised, crossover trial we investigated 8 clinically stable type 2 diabetic patients during an intravenous insulin or GLP-1 regimen to normalize blood glucose after a standardized breakfast.

Results: Time to reach a plasma glucose below 115 mg/dl, was significantly shorter during GLP-1 administration (252 ± 51 vs. 321 ± 43 min, $p<0.01$). Maximum glycemia (312 ± 51 vs. 254 ± 48 mg/dl, $p<0.01$), glycemia after 2 hours (271 ± 51 vs. 168 ± 48 mg/dl, $p=0.012$) and after 4 hours (155 ± 51 vs. 116 ± 27 md/dl, $p=0.02$) were significantly lower during GLP-1 administration.

Conclusions: GLP-1 infusion is superior to an established insulin infusion regimen with regard to effectiveness and practicability

Admission hyperglycemia is associated with an increased morbidity and mortality in diabetic and non-diabetic patients hospitalized for acute critical conditions (1,2). Several intervention studies in patients with acute myocardial infarction or cardiac surgery, using intravenously administered regular human insulin, suggest that normalization of hyperglycemia reduces morbidity as well as mortality in these patients (3,4,5,6). Insulin-based regimens, however, require frequent blood glucose measurements and adjustments of infusion rate to achieve this goal. In addition, hypoglycaemia is a frequent and important side effect that has been shown to be associated with a worse outcome in patients hospitalised with acute coronary syndromes (7). Hypoglycaemia was also discussed as a reason for the worse outcome in the intensive group in the recent NICE trial (8).

Glucagon-Like-Peptide 1 (GLP-1) is an insulinotropic, glucagonostatic gastrointestinal hormone that lowers glucose at fixed rates of administration in a glycemia-dependent manner and therefore does not cause hypoglycemia (9).

The aim of our study was to compare for the first time efficacy and safety of intravenously administered GLP-1 with an established intravenous insulin regimen in clinically stable hyperglycaemic type 2 diabetic patients as a pilot trial for possible future investigations in patient populations with acute, critical conditions.

RESEARCH DESIGN AND METHODS

We performed a prospective, open, randomised, cross-over trial in 8 patients with type-2 diabetes. Self-measured fasting glucose level had to be > 150 mg/dl for inclusion into the study. Patients with heart failure > NYHA II, uncontrolled hypertension, impaired kidney function (creatinine>3 mg/dl), or acute infection were

excluded. The study was approved by the local ethics committee, was conducted following GCP, and signed informed consent was obtained from all participants. 6 patients had a history of coronary artery disease (2 strokes, 2 myocardial infarctions, 2 coronary artery bypass graftings, 2 coronary artery revascularizations). All patients were treated with oral antidiabetic drugs.

Investigations took place on two occasions separated by 7 ± 3 days. Patients were admitted for a one-day stay at the "Metabolism and Vascular Research Unit". After an overnight-fast patients received a standardized breakfast (634 kcal, 100g carbohydrates, 35g fat, 13,6g protein). Treatment started 30 minutes after the end of the test meal. Patients were randomised to either the insulin infusion protocol as used in the Munich registry (10) or a continuous GLP-1 infusion (CLINALFA, Laeufelingen, Switzerland) at a dose of 1.2 pmol/kg/min for 8 hours. Both groups received a concomitant glucose (10%) infusion at a rate of 30 ml/h and blood glucose measurements were performed every thirty minutes or at symptoms of hypoglycaemia. Primary outcome was the time to reach a plasma glucose below 115 mg/dl, secondary outcome parameters were plasma glucose after 2 and 4 hours as well as maximum glycemia, and the number of hypoglycaemic episodes. Differences of study variables were tested by using ANOVA for repeated measurements or paired Student's t-test.

RESULTS

We investigated 8 patients (5 male) with a mean age of 58.2 ± 2.3 years, a BMI of 24.4 ± 1.0 kg/m² and an HbA1c of $7.3\pm 0.7\%$. Glucose levels at start of infusion therapy were comparable on both days of investigation (Insulin: 252 ± 42 mg/dl, GLP-1: 244 ± 24 mg/dl).

The primary endpoint, namely the time to reach plasma glucose below 115 mg/dl, was

significantly shorter during GLP-1 administration (252 ± 51 min. versus 321 ± 43 min, $p<0.01$, Fig. 1). Maximum glycemia (312 ± 51 versus 254 ± 48 mg/dl, $p<0.01$), glycemia after 2 hours (271 ± 51 versus 168 ± 48 mg/dl, $p=0.012$) and after 4 hours (155 ± 51 versus 116 ± 27 md/dl, $p=0.02$) were significantly higher during insulin administration in comparison to GLP-1. Glycemia after 8 hours, at the end of the intervention was comparable between both regimens (Insulin: 110 ± 24 , GLP-1: 103 ± 22 mg/dl, $p=ns$). Serum insulin levels were generally lower during GLP-1 treatment (data not shown). One symptomatic hypoglycaemia occurred during insulin infusion (48 mg/dl) whereas no hypoglycaemia was noted in the GLP-1 regimen. Nausea was observed in one patient during GLP-1 infusion.

CONCLUSIONS

Our study for the first time compared an established insulin infusion regimen with a GLP-1-infusion regimen in non-fasted type 2 diabetic patients regarding the efficacy to normalize hyperglycemia.

We clearly showed that by the GLP-1-based regimen glucose targets could be achieved faster in comparison to the insulin regimen and that maximal glycaemic excursions were markedly reduced. Beside the advantage in time course of lowering hyperglycemia there is no need for frequent blood glucose measurements and subsequent dose adaptations as it is required by using intravenous insulin. Our pilot study, thus, indicates that GLP-1-based regimens should be further tested in acute clinical settings as e.g. in hyperglycemic patients with acute myocardial infarction or undergoing vascular surgery in whom hyperglycemia was shown to predict a worse outcome (1,2,3,4,5,6).

Up to now, blood glucose lowering in this setting is performed by variable insulin infusion protocols that may cause hypoglycemia. High rates of hypoglycemia, in

turn, are discussed as a possible explanation for the worse outcome of the intensive control arm (6.8% versus 0.5% in the conventional arm) in the NICE trial (8). In addition, Kosiborod and colleagues (7) recently showed that the relation between mean in-hospital blood glucose and mortality rate is J-shaped indicating that a low mean blood glucose or recurring hypoglycemic episodes are associated with worse outcome. With that regard, a GLP-1 regimen has the clear advantage not to cause hypoglycemia.

Preserved capacity of insulin secretion is important for adequate GLP-1 action, thus type 1 diabetic subjects as well as insulin treated type 2 diabetic patients might not respond sufficiently to GLP-1 infusion.

Since postprandial hyperglycemia is the main target for GLP-1, due to additional inhibitory effects on gastrointestinal motility, our study might overestimate the therapeutic potential (11). Previous studies, however could also demonstrate a clear beneficial effect of GLP-1 on fasting glycemia (12).

In summary the results of our pilot trial indicate that in hyperglycemic, clinically stable type-2 diabetic patients a GLP-1 based infusion regimen is superior to an insulin based regimen to reach normoglycemia regarding effectiveness and practicability. We suggest that GLP-1 based treatment strategies should be further tested in hyperglycemic patients under conditions of acute illness with regard to effectiveness as well as clinical endpoints.

DISCLOSURE

H. Sourij: no conflict of interest to disclose.

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Figure 1: Plasma glucose course by using the insulin regimen in comparison to the GLP-1 regimen.

