

Abstract

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Background/Aim: The aim of the present study was to evaluate a new insulin infusion algorithm allowing to safely reach and maintain normoglycemia without provoking severe and/or prolonged hypoglycemic episodes in patients with type 2 diabetes. Such procedures might help to rapidly estimate insulin requirements and to shorten the dose titration period for initiating or adjusting insulin treatment in patients with type 2 diabetes with varying degrees of insulin resistance

Patients and methods: 12 type 2 diabetic subjects (age 58 ± 8 y., BMI 32.8 ± 5.3 kg m², fasting plasma glucose 222 \pm 57 mg/dl, HbA₁₀ 10.7 \pm 1.6 %, diabetes duration 9 \pm 5 y., 9/3 f/m) participated. Insulin or oral antidiabetic treatment was stopped the evening prior to the test. The patients fasted after midnight. The insulin infusion started at 1 mU/kg/min at 8:00 a.m., Glucose was measured every 30 min and accordingly the infusion rate was adjusted. The algorithm uses relative changes in insulin infusion rates according to difference from the predefined target range (70 - 120 mg/dl) and rate of change in plasma glucose concentration during the last 30 min. Every 60 min blood was drawn for determining plasma insulin (IMx, Abbott).

<u>Results:</u> The blood glucose target range (70 – 120 mg/dl) was reached within 2.6 \pm 0.8 h. The lowest glucose level was 64 ± 13 mg/dl (range: 40 - 82 mg/dl) after 3.7 ± 1.0 h. Only in one patient, two consecutive measurements below 50 mg/dl were recorded. Steady state glucose concentration maintained for 3.0 \pm 0.8 h were 87 \pm 7 mg/dl (CV 7.1 \pm 4.3 %). Initial serum insulin concentrations were 17.9 + 10.6 mU/l. Maximum insulin infusion rates $(2.9 \pm 1.5 \text{ mU-kg}^{-1}\text{min}^{-1})$ were required after 1.7 ± 0.9 h Steady state insulin infusion rates $(0.47 \pm 0.35 \text{ mU kg}^{-1} \text{ min}^{-1})$ were reached by 4.0 \pm 1.3 h. The maximum serum insulin concentration (288.3 ± 205.0 mU/l) were reached approximately when reaching the glucose target range $(2.5 \pm 0.8 \text{ h})$ steady state concentrations of $46.8 \pm 32.9 \text{ mL}/l$ (range: 4.6 - 115.5 mU/l; CV 13.5 \pm 9.2 %) were reached after 4.5 \pm 1.0 h and were maintained for an additional 2.3 ± 1.1 h without any change in insulin infusion.

Conclusions: The present study shows that it is technically feasible to guide an insulin infusion by an algorithm that allows a rapid and rather safe approach and maintenance of normoglycemia in patients with type 2-diabetes and fasting hyperglycemia. The present methodology may be used whenever a rapid normalization of glycemia is needed. It may also help to rapidly estimate insulin requirements in patients with type 2-diabetes.

Results

The blood glucose target range (70 - 120 mg/dl) was reached within 2.6 ± 0.8 h. The lowest glucose level was 64 ± 13 mg/dl (range: 40 - 82 mg/dl) after 3.7 ± 1.0 h. Only in one patient, two consecutive measurements below 50 mg/dl were recorded. Steady state glucose concentration maintained for 3.0 ± 0.8 h were 87 ± 7 mg/dl (CV 7.1 ± 4.3 %) (Fig. 1A). C-peptide decreased parallel to plasma glucose from initial 3.4 ± 1.2

ng/ml to 1.2 ± 0.6 ng/ml during steady state (Fig. 1B). Maximum insulin infusion rates (2.9 ± 1.5 mU·kg⁻¹·min⁻¹) were required

after 1.7 ± 0.9 h. Steady state insulin infusion rates (0.47 ± 0.35 mU kg ¹ min⁻¹) were reached by 4.0 ± 1.3 h (Fig. 2A).

Initial serum insulin concentrations were 17.9 ± 10.6 mU/l. The maximum serum insulin concentration (288.3 ± 205.0 mU/l) were reached approximately when reaching the glucose target range (2.5 \pm 0.8 h). Steady state concentrations of 46.8 ± 32.9 mU/l (range: 4.6 - 115.5 mU/l; CV 13.5 ± 9.2 %) were reached after 4.5 ± 1.0 h and were maintained for an additional 2.3 ± 1.1 h without any change in insulin infusion (Fig. 2B).

As expected, insulin infusion rates correlated with the insulin concentration during steady state (Fig. 3).

A safe algorithm for reaching and maintaining normoglycemia through a feed-back infusion of insulin in patients with type 2 diabetes El-Ouaghlidi A., Rehring E., Fehse F., Kunze M., Nauck M.

Diabeteszentrum, D-37431 Bad Lauterberg im Harz, Germany; Phone: +49-5524-81305, Fax: +49-5524-81398, stoffwechsel@diabeteszentrum.de

Introduction

Rapid normalization of glycemia in type 2 diabetes is required e.g. prior to surgical or other invasive procedures or in preparation of research protocols. The optimal individual insulin dose may vary widely in type 2 diabetes with different degrees of insulin resistance and might also be influenced by the patients residual insulin secretion capacity.

In insulin infusion algorithms described up to now the insulin requirement was extrapolated using a glucose controlled (every 30 - 60 minutes) feed back insulin infusion over night aiming at normal fasting blood glucose levels (1, 2). Mao et al. (1) could demonstrate a significant correlation between actually necessary and calculated insulin requirement (r = 0.88, p < 0.001) in a feed back insulin infusion. But in these studies the target alucose concentration could not be reached in all experiments.

Aim

Our aim was to evaluate a safe insulin infusion algorithm reaching and maintaining normoglycemia in type 2 diabetes reliably without provoking severe and/or prolonged hypoglycemic episodes. The present methodology may be used whenever a rapid normalization of glycemia is needed, e.g. prior to surgical or other invasive procedures or in preparation of research protocols.



Patients and Methods

12 obese subjects with insufficiently controlled type 2 diabetes (demographic data see Table 1) underwent an intravenous feed back insulin infusion. The day prior to feed back insulin infusion antidiabetic drugs and basal insulin (last dose in the morning), and/or regular insulin (last dose 18:00) were discontinued to avoid interferences with the test procedure. The participants fasted after midnight, carbohydrate free beverages were allowed. The insulin infusion (1 U Actrapid®/ml NaCl 0.9 %) was commenced (1 mU kg⁻¹ min⁻¹) at 8:00 a.m.. The infusion rate could be adjusted in steps of 0.1 ml/h (equivalent to 0.1 U/h insulin).

Capillary plasma glucose was measured every 30 min aiming at 100 mg/dl (5.5 mmol/l) with a range of 70 - 120 mg/dl (3.9 - 6.7 mmol/l). For the actual plasma glucose (PG₂) 7 intervals were defined within which different relative changes in insulin infusion rate were made according to the rate of change in plasma glucose concentration during the last 30 min (PG₂-PG₂) (Table 2). Every 60 min blood was drawn for determining plasma insulin and C-peptide. The insulin infusion was stopped when the plasma glucose remained within the euglycemic target range for at least 2 h under a constant insulin infusion rate (steady state).

Plasma glucose was measured using the glucose oxidase method at the Beckman Glucose Analyser 2 (Beckman Instruments GmbH. Munich. Germany). Insulin (IMx, Abbott, Wiesbaden, Germany) and C-peptide (Adaltis Deutschland GmbH, Freiburg, Germany) were determined using ELISA technic.

Calculation of the required insulin infusion rate was simplified by using a computer program.

Mao et al. (1, 2) using e.g. the same initial infusion rate. but differing in not using absolute but relative changes in insulin infusion rates according to the difference from the predefined target range and rate of

change in plasma glucose concentration. Therefore no assumptions are made beforehand regarding insulin sensitivity. Previous algorithms have led to higher glucose levels than aiming for (1, 2) and did not mediate a reduction in glucose concentrations into the target range in some cases (11%) (1).

The target range (70 - 120 mg/dl) was chosen lower than in comparable studies to avoid interferences with the bodies own alucose regulation. which resulted in some of the previous tests with a target range equal or above 80 mg/dl in not obtaining a steady state, because a continuous reduction of the insulin infusion rate was necessary when reaching glucose levels below the target range.

Discussion

This low base limit for the target range could potentially result in a higher risk for hypoglycemia. Actually, plasma glucose concentrations below 50 mg/dl were recorded in only one case and below 60 mg/dl solely in three cases. Strictly following the algorithm glucose concentrations were raised back into the target range within 30 to maximum 90 minutes without any additional interventions (e.g. glucose administration).









Figure 1: Plasma glucose (A) and C-peptid concentration (B) during feed-back insulin

Figure 2: Insulin infusion rate (A) and insulin concentration (B) during feed-back insulin infusion. (---) mean ± 95% CI (---), (---) individual data. N = 12.

Figure 3: Correlation analysis between insulin infusion rates and insulir concentration in steady state (a) during feed-back insulin infusion. r2: Correlation coefficient. N = 12

Conclusions

Our insulin infusion algorithm is modified from Mokan and Gerich and

The present study shows that it is technically feasible to guide an insulin infusion by an algorithm that allows a rapid and rather safe approach and maintenance of normoglycemia in type 2-diabetes with fasting hyperglycemia. The present methodology may be used whenever a rapid normalization of glycemia is needed, e.g prior to surgical or other invasive procedures or in preparation of research protocols.

References

- Mao et al. (1997): An overnight insulin infusion algorithm provides morning normoglycemia and can be used to predict insulin requirements in noninsulindependent diabetes mellitus. J Clin Endocrinol Metab 82: 2466 - 2470
- (2) Mokan et al (1992): A simple insulin infusion algorithm for establishing and maintaining overnight near-normoglycemia in type I and Type II Diabetes. J Clin Endocrinol Metab 74: 943 - 645

an ± SD n (%)	
58 ± 8	
2.8 ± 5.3	
9/3	
9 ± 5	
).7 ± 1.6	
22 ± 57	
8 (67)	
6 (50)	
4 (33)	
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Table 2: Criteria for insulin dose adjustment.

Actual plasma glucose (PG _a) [mg/dl]	∆ PG (PG _a -PG _{a-1}) [mg/dl]	Dose adjustments [%]
> 180	> -20	+50
	≤ -20 - > -40	+30
	≤ -40	0
151 – 180	> -10	+50
	≤ -10 - > -30	+30
	≤ -30 - > -40	0
	≤ -40	-30
121 – 150	> -10	+30
	≤ -10 - > -20	+15
	≤ -20 - > -30	0
	≤ -30	-30
71 – 120	> 10	+15
	≤ 10 - > -10	0
	≤ -10 - > -20	-30
	≤ -20	-50
66 – 70	> 10	0
	≤ 10 - > -10	-30
	≤ -10	-50
61 – 65	> 20	-30
	≤ 20	-50
≤ 60		-50