Changes in Basal Insulin Infusion Rates with CSII: Time until a Change in Metabolic Effect is Induced in Patients with Type 1 Diabetes

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Running title: Metabolic effects of changing basal rates


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Aim: Evaluation of the time required until a change in the basal insulin infusion rate with an insulin pump induces subsequent changes in the metabolic effect.

Methods: In this euglycemic glucose-clamp study 10 male subjects with type 1 diabetes received 3 different SC insulin infusion rates (0.5, 1.0 and 2.0 U/h; for 4 h each) of insulin Lispro (IL) with insulin pumps.

Results: An increase in insulinemia occurred within 15-30 min after changing the infusion rate. While the serum IL levels reached a steady state at the end of the infusion period, the glucose infusion rates did not always reach steady state levels with the higher infusion rates. However, an increase in the glucose consumption occurred within 30-60 min after switching the infusion rate.

Conclusions: It requires several hours until a new steady state in the metabolic effect is achieved after a significant change in basal insulin infusion.

Abbreviations:
AUC_{GIR}, AUC of glucose infusion rate
AUC_{INS}, AUC of insulin concentration
CSII, continuous subcutaneous insulin infusion
GIR, glucose infusion rate
Depening on the therapeutic strategy patients on CSII are often instructed to vary their basal rates over 24 h in a specific pattern. Therefore, changes in insulin infusion are initiated at hourly intervals in many patients. Previous studies indicate that it takes 2-3 hours until a change of 0.5-1U in basal insulin infusion rates led to a relevant change in insulin absorption using regular insulin (1-3). The respective change in serum insulin levels has not been investigated at the same time. Aim of this study was to evaluate how rapidly changes in basal insulin infusion rates are reflected in circulating insulin levels and the respective metabolic effect when infusing a rapid-acting insulin analogue.

RESEARCH DESIGN AND METHODS

This was an open-label, randomized, mono-center euglycemic glucose clamp study with two identical study days except for the insulin pumps used. Ten male patients with type 1 diabetes were enrolled (age 41±9 years; BMI 25.2±2.4 kg/m²; HbA₁c 7.1±0.4%; four on CSII; total daily insulin dose 57±13 IU, 0.68±0.12 IU/kg BW). This study was performed according to GCP-guidelines, including informed consent.

On both study days identical and stable glycemia (blood glucose (BG) target 6.0 mmol/L) and insulinemia (basal IV infusion of regular human insulin (RHI) 0.2 mU/kg/h) were established overnight by an automated glucose clamp. In the morning a SC infusion of insulin Lispro (IL) with commonly used insulin pumps was established on the study days (Paradigm 522, MiniMed, Northridge, CA, USA; Accu-Chek Spirit, Roche Diagnostics, Mannheim, Germany). Use of different insulin formulations for IV and SC infusion allowed differentiation of insulin applied via the different infusion routes. After a baseline infusion rate (0.1 U/h for 4 h) the following infusion rates were applied (U/h; for 4 h each): 0.5, 1.0, and 2.0. The same infusion protocol was employed on both study days.

One of the two radio immunoassays used measured total insulin levels (IL and RHI), the other RHI only. Serum IL levels were calculated from the difference between the measurements. The time required until glucose infusion rates (GIR) reached a new steady state level was evaluated during each of the three infusion periods. Free fatty acid (FFA) levels were measured in the blood samples as a secondary sensitive measure for insulin action with a standard method.

The summary measures obtained were compared by means of a paired t-test. Due to the fact that no significant differences between the two study days were observed, the combined data of both study days were presented.

RESULTS

Mean BG was kept constant throughout the infusion periods (6.0±0.1 mmol/L (CV 2%) (Figure 1a). IV infusion of RHI throughout the experiments established stable serum insulin levels (79±5 pmol/L; Figure 1b). Serum IL levels increased during the 0.5 U/h infusion period from 21±19 to 28±16 pmol/L (mean±SD; p<0.01 vs. baseline; Figure 1c). With an infusion rate of 1.0 U/h nearly a doubling of the IL levels was observed (to 54±20; p<0.001 vs. end of 0.5 U/h). An increase in insulinemia occurred within 15-30 min after switching of the infusion rate. With an infusion rate of 2.0 U/h another twofold increase in insulinemia took place (to 107±27 pmol/L; p<0.001 vs. end of 1.0 U/h). Insulinemia
reached a steady-state level in the last 120 min within the 0.5 and 1.0 U/h infusion period, but with an infusion rate of 2.0 U/h no steady state was achieved but there still was an increase after 4 hours.

GIR showed no significant increase during the infusion of 0.5 U/h (from 0.1±1.0 to 0.3±2.5 mg/kg/min; NS); however, with a doubling of the infusion rate to 1.0 U/h (to 1.7±2.5 mg/kg/min; p<0.001) and again to 2.0 U/h (to 3.8±3.5 mg/kg/min; p<0.02) such an increase was registered (Figure 1d). This increase occurred within 30-60 min after switching of the infusion rate. GIR reached a steady state in the last 120 min of the 0.5 and 1.0 U/h infusion period, but not with the infusion rate of 2.0 U/h. FFA levels remained stable during the infusion period with 0.5 U/h (Figure 1e). However, with the further increase in insulinemia FFA levels were suppressed by 65%.

**CONCLUSIONS**

This study indicates that it takes 2.5-4 h until a considerable change in basal infusion rate (0.5-1.0 U/h) leads to a new steady state level in the induced metabolic effect even if a rapid-acting insulin analogue is infused. Research on peak action of insulin boluses revealed that it takes 60 min until insulin and 100 min until GIR reach maximum levels (4). Similar changes of basal insulin infusion have also been evaluated employing cessation of insulin delivery. It has been disclosed that with IL, metabolic changes occurred within 1 hour after termination insulin infusion and were clearly demonstrated after 3 hours (5-7). In daily practice, the hourly basal rate pattern most often is not varied to this extent from hour to hour but is adjusted in smaller steps as shown for instance in children and adolescents (8). The different basal rates in this study were chosen to demonstrate substantial changes in insulinemia, glucose consumption and FFA levels. However, a longer evaluation period of 5-6 h would have been more appropriate to demonstrate that new steady state levels were reached.

Considering the observed delay after a significant change of the basal rate, the time gap before achieving a new stable metabolic effect should be taken into account when modifying the basal rate. There is a good body of clinical experience indicating that individual basal insulin adjustment via CSII is the best manner to cover basal insulin requirements. The data presented here indicate that the options of modern insulin pumps need adequate coordination and fine tuning with the metabolic effect. The observed delay also has to be considered when stopping the insulin infusion to avoid or to attenuate the development of a hypoglycemic event (5,7).

In summary, significant changes in basal insulin infusion rates with CSII might require several hours until a new stable metabolic effect level is reached. This topic should be systematically evaluated in greater detail within clinical trials.

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Legend for Figure 1
Mean (±SE) glycemia (a.), serum human insulin (b.), serum insulin Lispro (c.), glucose infusion rates (d.; with baseline correction), and free fatty acids levels (e.) measured in 10 male subjects with type 1 diabetes with three different basal SC insulin infusion rates (0.5, 1.0 and 2.0 U/h) in addition to a baseline IV infusion of regular human insulin (0.2 mU/kg/min).
REFERENCES


Figure 1

Figure 1a.

Figure 1b.
Figure 1c.

serum insulin Lispro (pmol/L)

0.5 U/h

1.0 U/h

2.0 U/h

time (min)

Figure 1d.

glucose infusion rate (mg/kg/min)

0.5 U/h

1.0 U/h

2.0 U/h

time (min)
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Figure 1e.

Free fatty acids (mmol/L)

0.4

0.3

0.2

0.1

0.0

0 60 120 180 240 300 360 420 480 540 600 660 720

Time (min)

0.5 U/h

1.0 U/h

2.0 U/h