Changes in Basal Insulin Infusion Rates With Subcutaneous Insulin Infusion

Time until a change in metabolic effect is induced in patients with type 1 diabetes

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OBJECTIVE — 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.

RESEARCH DESIGN AND METHODS — In this euglycemic glucose clamp study, 10 male subjects with type 1 diabetes received three different subcutaneous insulin infusion rates (0.5, 1.0, and 2.0 units/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 — Several hours are required until a new steady state in the metabolic effect is achieved after a significant change in basal insulin infusion.

Diabetes Care 32:1437–1439, 2009

Depending on the therapeutic strategy, patients on continuous subcutaneous insulin infusion (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 h until a change of 0.5–1 units of regular insulin in basal insulin infusion rates leads to a relevant change in insulin absorption using regular insulin (1–3). The respective change in serum insulin levels has not been investigated simultaneously. The 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 analog.

RESEARCH DESIGN AND METHODS

— This was an open-label, randomized, monocenter euglycemic glucose clamp study with 2 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/m^2; A1C 7.1 ± 0.4%; four on CSII; total daily insulin dose 57 ± 13 IU, 0.68 ± 0.12 IU/kg body wt). This study was performed according to good clinical practice guidelines, including informed consent.

On both study days, identical and stable glycemia (blood glucose target 6.0 mmol/l) and insulinemia (basal intravenous [IV] infusion of regular human insulin [RHI] 0.2 mU · kg^{-1} · min^{-1}) were established overnight by automated glucose clamps. On both study mornings, subcutaneous (SC) infusions of insulin lispro (IL) with the commonly used insulin pumps Paradigm 522 (MiniMed, Northridge, CA) and Accu-Chek Spirit (Roche Diagnostics, Mannheim, Germany) were established. Use of different insulin formulations for IV and SC infusions allowed differentiation of insulin applied via the two infusion routes. After a baseline infusion rate (0.1 units/h for 4 h), the following infusion rates were applied (units/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 radioimmunoassays used measured total insulin levels (IL and RHI); the other measured RHI only. Serum IL levels were calculated from the difference between the measurements. The time required until glucose infusion rates (GIRs) 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 Student's *t* test. Because no significant differences between the 2 study days were observed, the combined data of both days were presented.

RESULTS

— Mean blood glucose was kept constant throughout the infusion periods (6.0 ± 0.1 mmol/l; coefficient of variation 2%) (Fig. 1*A*). IV infusion of RHI throughout the experiments established stable serum insulin levels (79 ± 5 pmol/l) (Fig. 1*B*). Serum IL levels increased during the 0.5 units/h infusion period from 21 ± 19 to 28 ± 16 pmol/l (means ± SD; $P < 0.01$ vs. baseline) (Fig. 1*C*). With an infusion rate of 1.0 units/h, nearly a doubling of the IL levels was observed (to 54 ± 20 pmol/l; $P < 0.001$ vs. end of 0.5 units/h). An increase in insulinemia occurred within 15–30 min after switching the infusion rate. With an infusion rate of 2.0 units/h, another twofold increase in insulinemia took place (to 107 ± 27 pmol/l; $P < 0.001$ vs. end of 1.0

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Received 26 March 2009 and accepted 15 May 2009.
Published ahead of print at http://care.diabetesjournals.org on 1 June 2009. DOI: 10.2337/dc09-0595.
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units/h). Insulinemia reached a steady-state level in the last 120 min within the 0.5 and 1.0 units/h infusion period. No steady state was achieved with an infusion rate of 2.0 units/h, but there still was an increase after 4 h.

GIR showed no significant increase during the infusion of 0.5 units/h (from 0.1 ± 1.0 to 0.3 ± 2.5 mg $\cdot$ kg^{-1} $\cdot$ min^{-1}; NS); however, with a doubling of the infusion rate to 1.0 units/h (to 1.7 ± 2.5 mg $\cdot$ kg^{-1} $\cdot$ min^{-1}; $P < 0.001$) and again to 2.0 units/h (to 3.8 ± 3.5 mg $\cdot$ kg^{-1} $\cdot$ min^{-1}; $P < 0.02$), such an increase was registered (Fig. 1*D*). This increase occurred within 30–60 min after switching the infusion rate. GIR reached a steady state in the last 120 min of the 0.5 and 1.0 units/h infusion period but not with the infusion rate of 2.0 units/h. FFA levels remained stable during the infusion period with 0.5 units/h (Fig. 1*E*). However, the further increase in insulinemia suppressed FFA levels 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 units/h) leads to a new steady-state level in the induced metabolic effect even if a rapid-acting insulin analog 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 h after termination of insulin infusion and were clearly demonstrated after 3 h (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 in 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

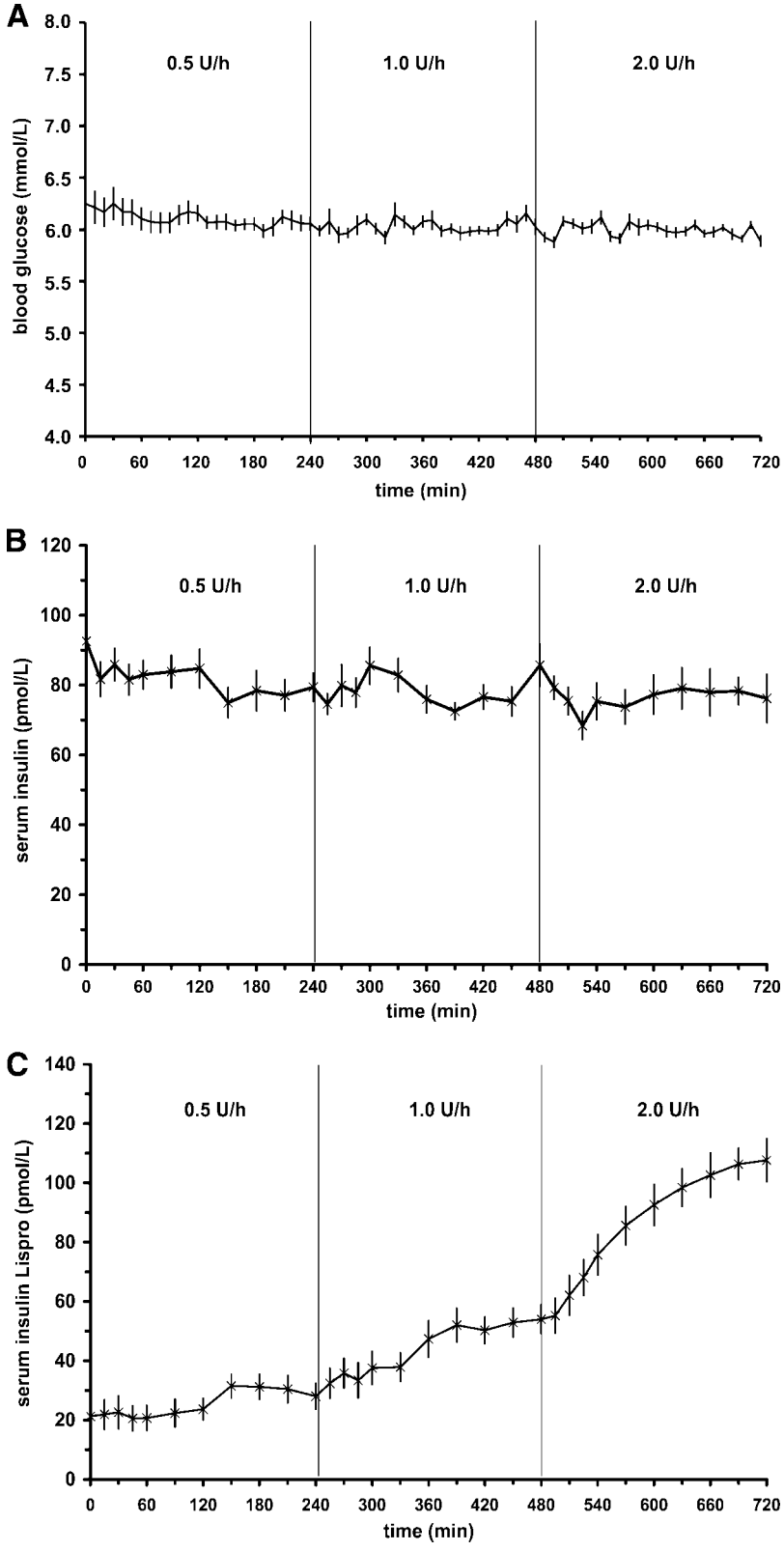

Figure 1—*Means ±SE glycemia* (A)*, serum human insulin* (B)*, serum IL* (C)*, GIRs* (D; *with baseline correction), and FFA levels* (E) *measured in 10 male subjects with type 1 diabetes with three different basal SC insulin infusion rates (0.5, 1.0, and 2.0 units/h), in addition to a baseline IV infusion of RHI (0.2 mU* $\cdot$ *kg*$^{-1}$ $\cdot$ *min*$^{-1}$*).*

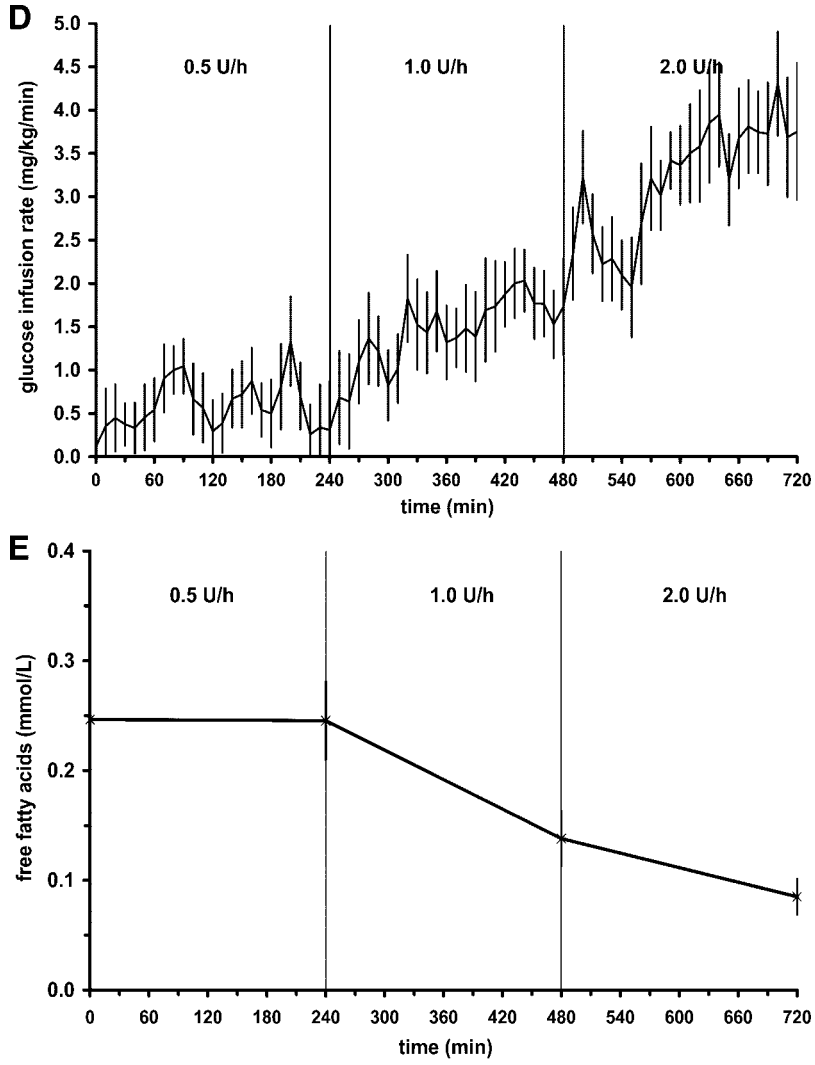

Figure 1—*Continued.*

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.

Acknowledgments— This study was supported by an unrestricted research grant by Roche Diagnostics GmbH, Mannheim, Germany. L.H. is a member of an advisory board of Roche Diagnostics GmbH. Disetronic Medical Systems AG is the manufacturer of one of the insulin pumps used in this study. No other potential conflicts of interest relevant to this article were reported.

Parts of this study were presented in abstract form at the 69th Scientific Sessions of the American Diabetes Association, New Orleans, Louisiana, 5–9 June 2009.

We thank the members of the European Infusion Systems Working Group (E. Renard, France, R.P.L.M. Hoogma, The Netherlands, S.Matthaei, Germany, T. Pieber, Austria, and D. Kerr, U.K.) for their support in planning and analyzing the study.

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