Safety of Insulin Glulisine when Given by Continuous Subcutaneous Infusion Using an External Pump in Patients with Type 1 Diabetes

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Abstract

This twelve-week, European, multicenter, controlled, open-label, randomized (1 : 1), parallel-group trial compared the safety of insulin glulisine with insulin aspart used in continuous subcutaneous insulin infusion. Patients with type 1 diabetes (n = 59) and continuous subcutaneous insulin infusion experience (mean values: HbA_{1c} 6.9 % [insulin glulisine: 6.8 % *vs.* insulin aspart: 7.1 %]; age 45.8 years; body mass index 26.0 kg/m^2) were enrolled. HbA_{1c} levels at endpoint (insulin glulisine: 7.0 % *vs.* insulin aspart: 7.2 %), daily insulin doses, blood glucose profiles and adverse event rates were similar in both groups. The median (minimum–maximum) catheter occlusion rate was low for insulin glulisine and insulin aspart (0 [0 – 0.7] *vs.* 0 [0 – 1.1] occlusions/month. Unexplained hyperglycemia occurred in six insulin glulisine-treated patients and twelve insulin aspart-treated patients. Patients were expected to change their catheters every 2 days (15 changes/month); the catheter change rate was similar for insulin glulisine and insulin aspart (14.1 *vs.* 14.8 changes/month). The frequency of infusion site reactions and hypoglycemia, and the time between catheter changes were similar for both insulin forms. Diabetic ketoacidosis was not reported. This study supports the safety of insulin glulisine in continuous subcutaneous insulin infusion administered via an external pump in type 1 diabetes.

Key words
Insulin aspart · hypoglycemia · hyperglycemia · catheter occlusion · adverse events

Introduction

Continuous subcutaneous insulin infusion (CSII) is based on a continuous subcutaneous infusion of insulin delivered via an external pump; therefore, basal insulin supply is better adapted to physiological needs with boli of insulin on demand for prandial coverage, which also provides more flexibility to insulin requirement. Rapid-acting insulin analogues such as insulin lispro, insulin aspart and insulin glulisine begin to act more rapidly with the effect fading sooner than regular human insulin (RHI) after subcutaneous injection, and are therefore currently preferred in patients with type 1 diabetes [1 – 8]. The number of patients using pumps to deliver their daily insulin is increasing, and is estimated to be over 130 000 individuals worldwide (more than 80 000 of these are in the USA) [9].

Insulin glulisine is a novel, rapid-acting insulin analogue that exhibits a similar time-action profile to insulin lispro [10]. It is similar to human insulin except for the replacement of asparagine with lysine at position B3, and the replacement of lysine with glutamic acid at position B29 on the B-chain of the human insulin molecule. Insulin glulisine takes effect more rapidly, peaking earlier and fading sooner than RHI [10,11]. Insulin glulisine differs from other insulin analogues in that it does not require additional zinc to stabilize the preparation.

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The faster onset and shorter duration of action compared with RHI [10,11] suggest that rapid-acting insulin analogues would be highly suited in CSII. Indeed, previous studies have shown that the use of rapid-acting insulin analogues (insulin lispro) can improve glycemic control in CSII without an increased risk of hypoglycemia compared to RHI in patients with type 1 diabetes [4,12].

This study was performed to demonstrate that insulin glulisine may be safely administered by CSII via an external pump to control hyperglycemia in patients with type 1 diabetes. The study was designed to assess whether the physicochemical properties of insulin glulisine are compatible with pump use rather than testing for actual efficacy. The comparator used in the study was insulin aspart.

Materials and Methods

Patients

Patients eligible to participate in the study were male or female and aged >18 years, with type 1 diabetes and HbA_{1c} less than or equal to 8.5 %. All patients had been receiving insulin therapy for at least one year prior to study entry, with at least six months of CSII treatment immediately prior to the study. Patients had used the same type of external pump (MiniMed programmable pump, Disetronic H-Tron Plus V100, Disetronic D-Tron) for at least three months prior to study entry. Patients with a history of serious Ketosis episodes requiring hospitalization or abscess at the infusion site within the three months prior to study entry were excluded from enrolment.

Study design

The study had an open-label, multicenter, randomized (1 : 1; centralized procedure), controlled, parallel-group design, and was conducted in accordance with Good Clinical Practice and the ethical principles of the Declaration of Helsinki. All study documentation was reviewed and approved by an independent Ethics Committee. Prior to screening and before admittance to the study, all patients gave their written informed consent.

Study protocol

The study consisted of a one-week screening phase, a four-week run-in phase in which all patients received insulin aspart, and a twelve-week treatment phase. During the treatment phase, patients were administered a basal rate of insulin in addition to bolus doses of insulin glulisine or insulin aspart immediately before meals using CSII. Bolus doses and the basal infusion rate were adjusted according to the opinion of the investigator and the needs of the individual in order to achieve treatment goals of fasting and pre-prandial blood glucose concentrations of 5.0 – 6.7 mmol/l (90 – 120 mg/dl), and two-hour postprandial (two hours after the start of a meal) blood glucose concentrations of 6.7 – 8.9 mmol/l (120 – 160 mg/dl), all without encountering hypoglycemia.

Full instructions on use of the study equipment were given. Patients were trained to fill the pump reservoir, to use the infusion set and to insert the catheter. Patients were then instructed to change the infusion set and reservoir every 2 days (15 changes per month).

Objectives

The primary objective of the study was to evaluate the compatibility of insulin glulisine with pump use by specifically comparing the safety of insulin glulisine and insulin aspart when used in external pumps in terms of specific external pump parameters: catheter occlusions, rate of catheter changes, time interval between catheter changes, infusion site reactions and unexplained hyperglycemia. Secondary objectives were to compare the effects of insulin glulisine and insulin aspart treatments on blood glucose parameters: glycated hemoglobin (GHb; measured as HbA_{1c} equivalents), hypoglycemia, insulin doses, adverse events, laboratory data and vital signs.

Measurement of glycated hemoglobin

Glycated hemoglobin (GHb) was measured at the Diabetes Diagnostic Laboratory (certified by the National Glycohemoglobin Standardization Program) using affinity chromatography. Results are reported as 'HbA_{1c} equivalents' as used in the Diabetes Control and Complications Trial (DCCT) [13].

Study assessments

Any catheter occlusions or leakage of the infusion set were recorded in each patient's diary, together with the date and time of change of the infusion set (both planned and forced). Episodes of unexplained hyperglycemia, defined as blood glucose concentrations above 19.4 mmol/l (> 350 mg/dl) not due to any apparent medical, dietary, insulin dosing or pump failure were also noted. Symptomatic, nocturnal and severe symptomatic hypoglycemic episodes were all monitored in this study. Severe hypoglycemia was defined as an event with clinical symptoms resulting from hypoglycemia that required assistance from another person, confirmed by blood glucose less than 2.0 mmol/l (< 36 mg/dl), or with prompt recovery following oral carbohydrate, intravenous glucose or glucagon administration.

The study investigator observed patients for local or systemic treatment-emergent adverse events (TEAEs), and patients reported any such events that occurred during the study. Severe symptomatic hypoglycemia was systematically reported as a possibly related serious TEAE. Lipid levels, hematological parameters and clinical chemistry were also analyzed.

Statistics

No formal sample-size calculation was performed for this study. The intention-to-treat (ITT) population was defined as all randomized patients receiving study medication. Patients with missing baseline data or no value for a specific variable collected during the treatment phase were not included in statistical analysis for that variable. Mean differences between the two treatment groups were calculated and their corresponding 95 % confidence intervals (CI) provided for monthly rate of catheter occlusions, monthly rate of catheter changes, HbA_{1c} and blood glucose. A frequency distribution with the percentage difference between treatment groups and their 95 % CI was calculated for catheter occlusions; unexplained hyperglycemia; the proportions of patients with a decrease in HbA_{1c} from baseline values of at least

Table **1** Baseline characteristics

Characteristic	*Insulin glulisine (n = 29)*	*Insulin aspart (n = 30)*
Sex (male/female; n [%])	12 (41.4)/17 (58.6)	13 (43.3)/17 (56.7)
Age (years)*	44.8 ± 9.8	46.7 ± 12.3
BMI (kg/m^2)*	26.5 ± 4.7	25.5 ± 3.7
Time since diagnosis of diabetes (years)*	25.0 ± 12.6	27.2 ± 11.8
Age at diagnosis of diabetes (years)*	20.4 ± 15.3	19.9 ± 9.0
Duration of previous insulin treatment (years)*	24.9 ± 12.7	27.0 ± 11.7
Patients with ≥ 1 diabetic complication (n, [%])	19 (65.5)	19 (63.3)
HbA_{1c} (%)*	6.8 ± 0.7	7.1 ± 0.7
Daily bolus insulin dose (IU)†	21.4	20.0
Daily basal insulin dose (IU)†	21.4	22.8
Type of insulin pump used at study entry		
MiniMed programmable‡	7 (24.1)	11 (36.7)
Disetronic H-TRON plus V100	20 (69.0)	19 (63.3)
Disetronic D-Tron	2 (6.9)	0 (0.0)

* Mean ± standard deviation; † mean; ‡ MiniMed models 506, 507, 507c, and 508 were used; BMI, body mass index.

0.7% at week 12 and endpoint; fasting blood glucose and symptomatic hypoglycemia.

Laboratory values and vital signs were analyzed at baseline using analysis of variance (ANOVA) with treatment and center (pooled) as fixed effects. Changes from baseline to week 12 and to endpoint were evaluated using analysis of covariance (ANCOVA) with treatment and center (pooled) as fixed effects and the corresponding baseline value as covariate.

Results

Patients

This multicenter study was performed at eight centers in three European countries: France (3 centers; 17 patients), Germany (3 centers; 31 patients) and The Netherlands (2 centers; 24 patients). A total of 72 patients entered the screening phase, during which thirteen patients were withdrawn. The reasons for these withdrawals were: the patient no longer met the study criteria (n = 7), the patient did not wish to continue (n = 4), lack of efficacy with insulin aspart (n = 1), and hypoglycemia (n = 1). A total of 59 patients were randomized to insulin glulisine (n = 29) or insulin aspart (n = 30). All of these patients received study medication and comprised the ITT population.

During the treatment phase, two patients withdrew (one patient in the insulin glulisine group following a suicide attempt, and one patient in the insulin aspart group that did not wish to continue). The median duration of treatment during the treatment phase was 85 days in both treatment groups.

Baseline characteristics

Baseline characteristics for all patients are presented in Table **1**. No notable between-treatment differences were observed.

Catheter occlusions or changes

All 59 patients were included in the analysis of catheter occlusions. The rates and numbers of catheter occlusions reported during the treatment phase are presented in Table **2**.

During the treatment phase, four patients (13.8%) in the insulin glulisine group reported at least one catheter occlusion compared with eight patients (26.7%) in the insulin aspart group. Although not statistically significant, this was associated with a treatment difference of – 12.9% in favor of insulin glulisine (95% CI: – 33.1, 7.3). The median (minimum-maximum [mean]) rate of catheter occlusions per month was 0 (0 – 0.7 [0.1 ± 0.2]) for insulin glulisine and 0 (0 – 1.1 [0.2 ± 0.3]) for insulin aspart, and, although not statistically significant, was associated with a treatment difference of – 0.1 in favor of insulin glulisine (95% CI: – 0.2, 0.1). The time between catheter changes was similar for patients with catheter occlusions and those without. The mean rate of catheter changes was also similar for the two treatment groups (14.1 *vs.* 14.8 changes/month for insulin glulisine and insulin aspart, respectively). The mean time between catheter changes was 2.1 ± 0.3 days (range 1.6 – 3.4 days) for insulin glulisine and 2.0 ± 0.2 days (range 1.4 – 2.7 days) for insulin aspart.

Unexplained hyperglycemia

At least one instance of unexplained hyperglycemia was reported for six patients (20.7%) receiving insulin glulisine and twelve patients (40.0%) receiving insulin aspart. None of these cases were

Table **2** Catheter occlusions for the treatment phase

Variable	*Insulin glulisine (n = 29)*	*Insulin aspart (n = 30)*	*Difference: insulin glulisine minus insulin aspart % or mean*	*95% CI*
Patients with ≥ 1 catheter occlusion*	4 (13.8)	8 (26.7)	– 12.9	(– 33.1; 7.3%)
Rate of occlusions per month†	0 (0 – 0.7)	0 (0 – 1.1)		
Patients with no catheter occlusions*	25 (86.2)	22 (73.3)	–	–
Patients with 0 – 1 catheter occlusion/month*	4 (13.8)	7 (23.3)	–	–
Patients with 1 – 3 catheter occlusions/month*	0	1 (3.3)	–	–
Patients with > 3 catheter occlusions/month*	0	0	–	–

* n (%); † median (range); CI = confidence interval.

associated with diabetic ketoacidosis. In one patient receiving insulin aspart, hyperglycemia was associated with a catheter occlusion.

Glycemic control

Both treatment groups showed a slight increase in mean HbA_{1c} over the study period, with a mean change from baseline to endpoint of 0.2% (from 6.8% to 7.0%) in the insulin glulisine group and 0.1% (from 7.1% to 7.2%) in the insulin aspart group with a between-treatment difference of 0.11 (95% CI: – 0.09, 0.31). Self-monitored seven-point blood glucose variables showed no notable differences between treatment groups for any measurements throughout the study (data not shown).

Hypoglycemia

The number of hypoglycemic episodes and the proportion of patients experiencing hypoglycemic episodes are presented in Table **3**. Few patients reported severe symptomatic hypoglycemia in either group, and numbers were similar.

Insulin dose and regimen

The mean total daily insulin dose was similar for both insulin glulisine and insulin aspart at baseline (42.8 *vs.* 42.9 IU) and at endpoint (43.3 *vs.* 44.4 IU) with a treatment difference of – 1.1 (95% CI: – 4.8, 2.7). Mean daily bolus insulin dose increased slightly in both groups (+ 1.0 IU for insulin glulisine and + 1.5 IU for insulin aspart). Mean daily basal insulin dose decreased by 0.48 IU in the insulin glulisine group, but was relatively unchanged in the insulin aspart group (+ 0.09 IU).

Treatment emergent adverse events

Treatment emergent adverse events occurred in 14 (48.3%) and 20 (66.7%) patients receiving insulin glulisine and insulin aspart, respectively. Five patients (17.2%) experienced serious adverse events in the insulin glulisine group, compared with four (13.3%) patients in the insulin aspart group; none of the serious nonhypoglycemia adverse events were deemed to be possibly related to study medication.

One case of injection site inflammation and injection site pain was reported in each treatment group. In the insulin glulisine group, there was one case of injection site pruritus, which was possibly treatment-related. There were no significant differences in hematology, clinical chemistry, body weight or vital signs between the treatment groups at baseline or at endpoint.

Table **3** Symptomatic hypoglycemia episodes during the treatment phase

Hypoglycemia	*Insulin glulisine n (%)*	*Insulin aspart n (%)*
All symptomatic	26 (89.7)	24 (80.0)
Severe	2 (6.9)	2 (6.7)
Nocturnal	20 (69.0)	15 (50.0)

n = number of patients experiencing ≥ 1 episode of hypoglycemia.

Discussion and Conclusions

The main purpose of this study was to compare the safety of insulin glulisine (a new rapid-acting insulin analogue) with insulin aspart (approved for use in pump therapy) when used in CSII. Rapid-acting insulin analogues have been developed for use in multiple daily injection regimens and regimens that include subcutaneous injection in combination with CSII, and therefore require careful evaluation to ensure their compatibility with CSII. In particular, catheter occlusions could cause rapid increases in glycemia with the use of rapid-acting insulin analogues in CSII compared with regular insulin [14].

In this study, there was a low and similar rate of catheter occlusions in both the insulin glulisine and insulin aspart treatment groups, and the overall rate of catheter changes (both planned and forced) was also similar in both groups. Insulin glulisine-treated patients did show a trend towards fewer catheter occlusions compared with insulin aspart-treated patients (which may be explained by zinc-free formulation with polysorbate 20 as a detergent, which reduces the likelihood of surface-to-insulin interaction and thus contributes to reducing fibrillation and clotting); however, the limited sample size of the study prevents definitive conclusions regarding superiority to be drawn. Although this was a relatively short study, it was of similar or longer duration than comparable studies conducted with other rapid-acting insulin analogues [1 – 5, 8, 15]. However, the study was designed under the common assumption that the majority of catheter occlusions and adverse events will be observed within the first month of treatment.

There were fewer TEAEs in the insulin glulisine group compared with the insulin aspart group. Although serious adverse events were more frequent in the insulin glulisine group compared to insulin aspart, none of these were deemed to be possibly related to the study medication. In addition, there were no notable between-treatment differences in terms of injection site reactions or in the frequency of serious non-hypoglycemic TEAEs. Furthermore, there were no concerns about hypoglycemia reported as a serious TEAE, which occurred in a similar proportion of patients in both groups.

In conclusion, these data demonstrate that insulin glulisine can be safely used in CSII and does not have any adverse clinical implications for patients compared with another insulin analogue that has been approved for pump use in the USA and Europe. The results of this study, therefore, support the use of insulin glulisine in CSII therapy administered via an external pump.

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