Efficacy and safety of switching to insulin glulisine from other rapid-acting insulin analogs in children with type 1 diabetes

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ABSTRACT

We investigated the efficacy and safety of switching to insulin glulisine (GLU) from other rapid-acting insulin analogs (Ra) in children with type 1 diabetes treated with multiple daily injections of insulin or continuous subcutaneous insulin infusion. A total of 26 children with type 1 diabetes were included. Ra in all of these patients was changed to GLU, and they were observed for a 6-month period after having previously finished treatment with other Ra. The mean glycated hemoglobin value decreased from 7.6 ± 1.0 to 7.4 ± 0.9% (*P* = 0.0034), and mean plasma glucose values after breakfast and supper also improved from 183 ± 50 to 153 ± 32 mg/dL (*P* = 0.0035), and from 203 ± 29 to 164 ± 23 mg/dL (*P* < 0.0001), respectively. Furthermore, the mean frequency of hypoglycemia was reduced from 7 ± 6 to 4 ± 4/month (*P* = 0.0004), while insulin doses and obesity degree were stable with statistically non-significant differences. In conclusion, switching to GLU might be a good treatment option for improving glycemic control in children with type 1 diabetes.

INTRODUCTION

Three types of rapid-acting insulin analogs (Ra), insulin aspart (ASP), insulin lispro (LIS) and insulin glulisine (GLU), have a rapid onset of action within 30–60 min, and a peak action within 2 h to allow for appropriate control of postprandial glycemia[1]. In contrast, several studies have shown that GLU exhibits a faster onset of action, a shorter duration of action, and a similar or greater metabolic effect than ASP and LIS in adult patients with type 2 diabetes[2,3], and those with type 1 diabetes[4,5]. However, studies examining the efficacy and safety of GLU in pediatric patients with type 1 diabetes are quite limited[6,7]. We, therefore, studied the clinical usefulness of switching to GLU from other Ra in Japanese children with type 1 diabetes.

METHODS

The study consisted of 26 Japanese children with type 1 diabetes, 11 boys and 15 girls, aged 12.5 ± 5.5 years at the time of the study. None of the patients were identified as being obese with percent overweight exceeding 20%[8], and none had either vascular complications or metabolic-syndrome factors. They were treated with basal–bolus insulin therapy, with 18 patients using multiple daily injections of insulin (MDI) and eight patients using continuous subcutaneous insulin infusion (CSII). They previously used either ASP or LIS as bolus insulin for MDI or as a CSII preparation. Insulin glargine was used as basal insulin for MDI with a once- or twice-daily injection. Their mean values of fasting plasma glucose (FPG) and glycated hemoglobin (HbA1c; National Glycohemoglobin Standardization Program value)[9] were 117.7 ± 30.2 mg/dL and 7.63 ± 0.96%, respectively. The mean dose of total insulin was 0.84 ± 0.19 units/kg/day. Patients were instructed to adjust basal insulin doses to attain self-monitored PG levels before breakfast between 90 and 140 mg/dL[10], and to determine bolus insulin doses according to carbohydrate counting for both MDI and CSII.

ASP or LIS was switched to GLU for preparation of MDI or CSII with informed consent from both the patients and their parents before starting the study. Insulin glargine was continuously given as basal insulin for MDI as previously prescribed.

We evaluated changes in mean self-monitored values of PG just before, and 1–1.5 h after breakfast and supper for the 1-month period at baseline, and at 6 months after using GLU. We also evaluated changes in HbA1c, frequency of hypoglycemia for the 1-month period, daily insulin requirement, and percent overweight for at baseline and at 6 months after using GLU.

Mild hypoglycemia was defined as having clinical symptoms of hypoglycemia with or without self-monitored PG levels of 40–70 mg/dL. Severe hypoglycemia was defined as PG levels below 40 mg/dL with impaired consciousness or seizure necessitating assistance from other persons.

HbA1c levels were determined by high performance liquid chromatography, and expressed as National Glycohemoglobin Standardization Program values (normal: 4.6–6.1%).

The results were expressed as mean values ± standard deviation. Paired Student's *t*-test was used to detect the statistical significance of differences, and $P < 0.05$ was considered as a statistically significant difference.

RESULTS

Changes in Mean Values of PG and HbA1c at Baseline, and at 6 Months After Using GLU in all Patients

There were no significant differences in the mean values of PG before breakfast and supper after using GLU (Table 1). In contrast, those after breakfast and supper significantly improved from 183.4 ± 50.1 to 153.0 ± 32.2 mg/dL ($P = 0.0035$) and from 203.1 ± 29.3 to 163.8 ± 22.9 mg/dL ($P < 0.0001$), respectively. HbA1c significantly decreased from 7.63 ± 0.96 to 7.36 ± 0.93% after using GLU ($P = 0.0034$).

We also evaluated changes of these glycemic indicators in patients treated with MDI and CSII, separately. In patients treated with MDI, we identified no significant differences in the mean values of preprandial PG after using GLU, while those in postprandial PG significantly decreased from 170.3 ± 50.0 to 149.6 ± 34.5 mg/dL for breakfast ($P = 0.0427$) and from 197.3 ± 31.6 to 160.2 ± 24.0 mg/dL for supper ($P < 0.0001$). HbA1c decreased from 7.61 ± 0.96 to 7.37 ± 0.92% after using GLU, but the difference did not reach statistical significance. In patients using CSII, we also found no significant differences in

the mean values of preprandial PG after using GLU, while those in postprandial PG also significantly decreased from 205.7 ± 45.0 to 158.9 ± 29.5 mg/dL for breakfast ($P = 0.0434$) and from 214.8 ± 21.1 to 168.3 ± 19.9 mg/dL for supper ($P = 0.0002$). HbA1c decreased from 7.70 ± 1.03 to 7.33 ± 1.04% after using GLU, but the difference did not reach statistical significance.

Change in Frequency of Hypoglycemia, Mean Insulin Dose and Percent Overweight at Baseline and at 6 Months After Using GLU in all Patients

The frequency of mild hypoglycemia was significantly reduced from 7 ± 6 to 4 ± 4 times/month after using GLU ($P = 0.0004$; Table 2). No patients experienced severe hypoglycemia during the study period. There were no significant changes in total insulin dose, basal insulin dose and or obesity degree as assessed by percent overweight.

We also evaluated changes in these indicators in patients treated with MDI and CSII, separately. In patients treated with MDI, the frequency of mild hypoglycemia was significantly reduced from 5 ± 5 to 3 ± 3 times/month after using GLU ($P = 0.0127$). In patients using CSII, that was high at 10 ± 7 times/month before using CSII, but showed a clear decrease to 7 ± 6 times/month after using GLU ($P = 0.0108$). No patients experienced severe hypoglycemia during the study period, and there were no significant changes in the insulin doses given or in percent overweight in both MDI and CSII.

DISCUSSION

The International Diabetes Federation (IDF) has advocated that postprandial PG be measured 1–2 h after meals and that patients with diabetes maintain 1 to 2-h postprandial PG levels below 160 mg/dL without occurrence of hypoglycemia[11]. Taki *et al.*[12] showed that the mean peak times of postprandial PG in Japanese patients with type 1 diabetes were 100 min after breakfast, 65 min after lunch and 78 min after supper, based on a continuous glucose monitoring system. This result shows the importance of using Ra as bolus insulin, which suppresses the 1 to 2-h postprandial PG rise in patients with type 1 diabe-

Table 1 | Changes in mean values of plasma glucose and glycated hemoglobin at baseline and at 6 months after using insulin glulisine in all patients

	At baseline	After using GLU	P-value
PG before breakfast (mg/dL)	117.7 ± 30.2	116.6 ± 26.5	0.7104
PG after breakfast (mg/dL)	183.4 ± 50.1	153.0 ± 32.2	0.0035
PG before supper (mg/dL)	126.3 ± 33.0	122.8 ± 27.1	0.4175
PG after supper (mg/dL)	203.1 ± 29.3	163.8 ± 22.9	<0.0001
HbA1c (%)	7.63 ± 0.96	7.36 ± 0.93	0.0034

n = 26. HbA1c, glycated hemoglobin; GLU, insulin glulisine; PG, plasma glucose.

Table 2 | Changes in frequency of hypoglycemia, mean insulin dose and percent overweight at baseline and at 6 months after using insulin glulisine in all patients

	At baseline	After using GLU	P-value
Frequency of hypoglycemia (time/month)	7 ± 6	4 ± 4	0.0004
Total insulin dose (unit/kg/day)	0.84 ± 0.19	0.82 ± 0.16	0.3336
Basal insulin dose (unit/kg/day)	0.36 ± 0.18	0.35 ± 0.19	0.4812
Percent overweight (%)	6.86 ± 8.05	6.98 ± 7.61	0.7039

n = 26. GLU, insulin glulisine.

tes. In contrast, avoiding severe hypoglycemia in patients is also essential, particularly children and adolescents treated with insulin. Hypoglycemia potentially damages the central nervous system, and prevents patients from achieving target PG levels[13].

GLU is reported to have a faster onset of action and a shorter duration of action than ASP or LIS in patients with diabetes[2–5]. Becker et al.[14] indicated that GLU shows time to maximum insulin concentration at 57 min for patients with type 1 diabetes. This maximum insulin concentration time nearly corresponds to the peak time of postprandial glycemia[11,12]. Therefore, GLU as bolus insulin seems to be superior for controlling postprandial glycemia in patients with type 1 diabetes.

Several studies showed equivalent glycemic control and frequency of hypoglycemia between these Ra in patients with type 1 diabetes treated with either MDI[5,6,15,16] or CSII[17,18]. Nevertheless, we found GLU to be superior to other Ra for children with type 1 diabetes; that is, switching to GLU from ASP or LIS significantly decreased postprandial hyperglycemia to less than 160 mg/dL, which is recommended by the Guidelines of International Diabetes Federation 2011[11], and significantly reduced HbA1c levels to <7.5%, which is the target level in the Consensus Guidelines of International Society for Pediatric and Adolescent Diabetes 2009[10]. Furthermore, the frequency of hypoglycemia was significantly reduced, possibly because GLU synchronized postprandial glycemia without later glucose-lowering effects, which caused hypoglycemia between or before meals[1,15,16]. Such effectiveness was equally observed in patients treated with both MDI and CSII.

Superiority in improvement of glycemic control and reduction of frequency hypoglycemia in our patients after using GLU as compared with previous Caucasian studies[6,15–18] has some possible explanations. First, Japanese meals are known to traditionally have a higher carbohydrate energy ratio and a lower fat energy ratio than meals in Western countries. GLU has a faster onset of action than ASP and LIS, and could synchronize postprandial glycemia more with the consumption of carbohydrate-rich meals. Second, it has been reported that Japanese people showed slightly faster absorption and higher exposure with either Ra as compared with Caucasians, which might be explained by the leanness of Japanese people in general[12]. Third, children might be different from adults in regard to absorption and pharmacokinetics of insulin injected subcutaneously, which can potentially result in higher concentrations of insulin in children[19]. These factors could contribute a greater effect on lowering the PG rise and frequency of hypoglycemia with GLU in Japanese children as compared with Caucasians.

A limitation of the present study was the small number of children to evaluate the effect of GLU, therefore, it is necessary to confirm the present results in a large number of children with type 1 diabetes. Seasonal variations in HbA1c could influence the results.

In conclusion, using GLU rather than ASP or LIS with MDI and CSII might be a good treatment option for achieving optimal glycemic control without increasing the frequency of hypoglycemia in children with type 1 diabetes.

REFERENCES

1. Becker RH. Insulin glulisine complementing basal insulins: a review of structure and activity. *Diabetes Technol Ther* 2007; 9: 109–121.
2. Luzio S, Peter R, Dunseath GI, et al. A comparison of preprandial insulin glulisine versus insulin lispro in people with type 2 diabetes over a 12-h period. *Diabetes Res Clin Pract* 2008; 79: 269–275.
3. Bolli GB, Luzio S, Marzotti S, et al. Comparative pharmacodynamic and pharmacokinetic characteristics of subcutaneous insulin glulisine and insulin aspart prior to a standard meal in obese subjects with type 2 diabtes. *Diabetes Obes Metab* 2011; 13: 251–257.
4. Dreyer M, Prager R, Robinson A, et al. Efficacy and safety of insulin glulisine in patients with type 1 diabetes. *Horm Metab Res* 2005; 37: 702–707.
5. Kawamori R, Kadowaki T, Ishii H, et al. Efficacy and safety of insulin glulisine in Japanese patients with Type 1 diabetes mellitus. *Diabetes Obes Metab* 2009; 11: 891–899.
6. Philotheou A, Arslanian S, Blatniczky L, et al. Comparable efficacy and safety of insulin glulisine and insulin lispro when given as part of a basal-bolus insulin regimen in a 26-week trial in pediatric patients with type 1 diabtes. *Diabetes Technol Ther* 2011; 13: 327–334.
7. Danne T, Becker RHA, Heuse T, et al. Pharmacokinetics, prandial glucose control, and safety of insulin glulisine in children and adolescents with type 1 diabetes. *Diabetes Care* 2005; 28: 2100–2105.
8. Asayama K, Ozeki T, Sugihara S, et al. Criteria for medical intervention in obese children: a new definition of obesity disease in Japanese children. *Pediatr Int* 2003; 45: 642–646.
9. Kashiwagi A, Kasuga M, Araki E, et al. International clinical harmonization of glycated hemoglobin in Japan: from Japan Diabetes Society to National Glycohemoglobin Standardization Program values. *J Diabetes Invest* 2012; 3: 39–40.
10. Bangstad HJ, Danne T, Deeb L, et al. Insulin treatment in children and adolescents with diabetes. *Pediatr Diabetes* 2009; 10 (Suppl 12): 82–99.
11. IDF. 2011. Guideline for Management of PostMeal Glucose in Diabetes, www.idf.org.
12. Taki K, Nishimura R, Morimoto A, et al. Analysis of 24-hour glycemic excursions in patients with type 1 diabetes by using continuous glucose monitoring. *Diabetes Technol Ther* 2010; 12: 523–528.
13. Clark W, Jones T, Rewers A, et al. Assessment and management of hypoglycemia in children and adolescents with diabetes. *Pediatr Diabetes* 2009; 10(Suppl 12): 134–145.

14. Becker RHA, Frick AD. Clinical pharmacokinetics and pharmacodynamics of insulin glulisine. *Clin Pharmacokinet* 2008; 47: 7–20.

15. Helm KL, Kelly KW. Insulin glulisine: an evaluation of its pharmacodynamic properties and clinical application. *Ann Pharmacother* 2009; 43: 658–668.

16. Bartolo PD, Pellicano F, Scaramuzza A, *et al.* Better postprandial glucose stability during continuous subcutaneous infusion with insulin aspart compared with insulin lyspro in patients with type 1 diabetes. *Diabetes Technol Ther* 2008; 10: 495–498.

17. Weinzimer SA, Temand C, Howard C, *et al.* A randomized trial comparing continuous subcutaneous insulin infusion of insulin aspart versus insulin lispro in children and adolescents with type 1 diabetes. *Diabetes Care* 2008; 31: 210–215.

18. Hoogma PP, Schumicki D. Safety of insulin glulisine when given by continuous subcutaneous insulin infusion using an external pump in patients with type 1 diabetes. *Horm Metab Res* 2006; 38: 429–433.