

# Effects of Mixing Glargine and Short-Acting Insulin Analogs on Glucose Control

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Intensive insulin management improves glycemic control and lowers the risks of long-term microvascular complications (1). Several new insulin analogs (2) are in use to improve glycemic control in type 1 diabetes. Glargine in particular is a "basal insulin" (3) and found to be relatively peakless. Glargine is thought to provide glucose profiles similar to insulin pumps (4). Although some clinical studies suggest that glargine lasts 24 h in children with diabetes (5), to date there have been no formal pharmacokinetic and pharmacodynamic data to make that claim in the pediatric population. In fact, clinical observations in pediatric type 1 diabetes suggest that glargine action may be <24 h. This would entail twice-daily glargine dosing and short-acting insulin analogs (SAIs), such as lispro and aspart, given separately three to four times per day, resulting in improved glycemic control but compromising compliance and increasing complexity of management (6). In this study, we tested the hypothesis that mixing glargine with SAIs and dividing the dose of glargine into twice- versus once-daily dosing would not adversely affect glycemic control as assessed by a continuous glucose monitoring system (CGMS).

## RESEARCH DESIGN AND METHODS

The protocol was approved by the institutional review board of the Baylor College of Medicine, and consent was obtained before each study. Subjects were recruited from Texas Children's Hospital Diabetes Care Center,

Houston, Texas. Subjects had type 1 diabetes for at least 1 year with no other chronic illness and were on no additional medications (except for insulin and thyroid for hypothyroidism). All subjects were using insulin glargine as a once-daily injection at bedtime or before supper or breakfast, with three or more injections of SAIs (lispro or insulin aspart) administered with each meal. Subjects had HbA<sub>1c</sub> <9.0% and BMI <90th percentile for age. Each subject underwent three studies over a 4- to 6-week period.

Baseline study: subjects were studied on their baseline once-daily dose of glargine and three to four separate injections of SAIs that were dosed according to an insulin-to-carbohydrate ratio. After the baseline study, subjects were randomized into one of two groups with a crossover design. 1) Study separate: baseline dose of glargine divided into prebreakfast and predinner injections and SAI given with lunch. 2) Study mixed: same as study separate except that prebreakfast and predinner glargine and SAI were mixed in one syringe.

Study separate and mixed were implemented for 10 days, and continuous glucose monitoring was done on the final 3 days of each regimen. CGMS readings from the first day of monitoring were analyzed. If interruptions in readings occurred in the first 24-h period (this occurred in two subjects during the basal study), the following 24 h was chosen for analysis. Average 72-h glucose data were also compared.

The subjects were instructed on continuous glucose monitoring, and a CGMS sensor was inserted by study personnel. The subjects continued their normal insulin-to-carbohydrate ratio, sensitivity factor, diet, and exercise. Parents attempted to have consistency of meal times and physical activity throughout the study period. The children were monitored (at baseline and in the final 3 days of study separate and mixed) using the Mini-Med CGMS. CGMS calibrations with a glucose meter were performed four times daily. If the blood glucose values were <60 mg/dl for ≥30 min by CGMS or hypoglycemic symptoms were felt, subjects and/or the family completed a hypoglycemia record log and treatment instituted was noted. CGMS data were downloaded and analyzed using CGMS System Solutions Software. The mean blood glucose values 60 min before and 3 h after meal initiation were considered. Subjects were blinded to data.

## Statistical analysis

All data are presented as means ± SE. Repeated-measures ANOVA was used to determine the effects of treatment, order of treatment, and their interaction. Carry over and order of treatment effects were examined. Significance was considered at  $P = 0.05$  (two-tailed test).

**RESULTS**— A total of 14 subjects were recruited, and 1 subject did not comply with study regimens and was not considered in the analysis. Glargine was administered to nine subjects at bedtime, two subjects at dinner, and two subjects in the morning. This study was conducted in real-life conditions and, hence, CGMS was chosen as a tool for measuring glucose excursions. Mixing glargine with lispro and aspart resulted in cloudiness of the mixture. There was no difference in pain or reported adverse reactions to the mixed injections. Thirteen subjects (6 males and 7 females, aged  $13.5 \pm 0.5$  years, BMI  $22.4 \pm 1.0$  kg/m<sup>2</sup>, HbA<sub>1c</sub>  $7.7 \pm 0.2\%$ , and type 1 diabetes duration  $44 \pm 8$  months) were studied.

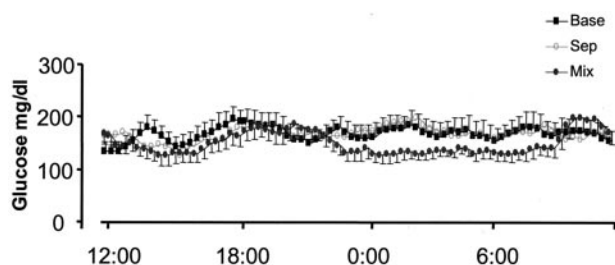
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**Abbreviations:** CGMS, continuous glucose monitoring system; SAI, short-acting insulin analog.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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**Figure 1**— Glucose values using a CGMS over a 24-h period. Comparison of the baseline (Base; ■), study separate (separate injections of glargine and SAIs [Sep]; ○), and study mixed (mixed injections of glargine and SAIs [Mix]; ●).

Figure 1 demonstrates CGMS-derived Q20-min glucose values over a 24-h period. Nocturnal blood glucose (12:00 A.M. to 6:00 A.M.) analyzed separately from 24-h blood glucose was not statistically different ( $P < 0.16$ ). On further analysis of nocturnal glucose concentrations, subjects in study mixed spent more time euglycemic than hyper- and hypoglycemic, but this was not statistically significant (Table 1).

Mean 24-h glucose values were  $9.3 \pm 1.3$ ,  $9.3 \pm 1.2$ , and  $8.3 \pm 1.1$  mmol/l ( $P < 0.6$ ) and mean 72-h glucose values  $9.1 \pm 0.5$ ,  $8.9 \pm 0.7$ , and  $8.4 \pm 0.5$  mmol/l ( $P < 0.3$ ) for baseline, study separate, and study mixed, respectively. No significant difference was noted in hypoglycemic episodes in a 24-h period (5, 9, and 2%). Furthermore, neither preprandial ( $8.8 \pm 9$ ,  $8.3 \pm 9$ , and  $8.2 \pm 19$  mmol/l) nor postprandial ( $9.6 \pm 17$ ,  $9.1 \pm 17$ , and  $9.0 \pm 19$  mmol/l) glucose concentrations differed between baseline, study mixed, and study separate, respectively.

**CONCLUSIONS**— This study provides preliminary data that mixing glargine with lispro or aspart insulin in the same syringe and dividing the dose of glargine does not adversely affect glucose concentrations. Lower nocturnal blood glucose concentrations in study mixed versus study separate and basal, although not statistically significant, should alert physicians that the evening dose of lantus may need to be titrated to prevent hypoglycemia. No serious adverse events occurred during the study. Although the mixtures turned cloudy, no complaints of increased pain or injection difficulties were reported. Long-term effects of mixing glargine and SAIs on HbA<sub>1c</sub> were not assessed in this study.

In conclusion, our data suggest that mixing glargine with SAIs or twice-daily dosing does not affect short-term glycemic profile. Further studies are needed to evaluate the long-term effects of these regimens.

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**Table 1**—Time spent in hypo- and hyperglycemic range between 12:00 a.m. and 6:00 a.m.

	Basal	Mixed	Separate	P
Hypoglycemia (average min/patient)	22 ± 17	20 ± 14	10 ± 9	NS
Hyperglycemia (average min/patient)	129 ± 41	47 ± 20	145 ± 37	NS
Euglycemia (average min/patient)	206 ± 39	292 ± 21	205 ± 35	NS

Data are means ± SE.