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 HbA1c <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 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 baseline study), the following 24 h was chosen for analysis. Average 72-h glucose data were also compared.

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 ± 0.5 years, BMI 22.4 ± 1.0 kg/m², HbA1c 7.7 ± 0.2%, and type 1 diabetes duration 44 ± 8 months) were studied.

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).
Can glargine and lispro be mixed?

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 ± 1.3, 9.3 ± 1.2, and 8.3 ± 1.1 mmol/l \((P < 0.6)\) and mean 72-h glucose values 9.1 ± 0.5, 8.9 ± 0.7, and 8.4 ± 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 \((5, 9, \text{and} 2\%)\).

Furthermore, neither preprandial \((8.8 ± 9, 8.3 ± 9, \text{and} 8.2 ± 19 \text{mmol/l})\) nor postprandial \((9.6 ± 17, 9.1 ± 17, \text{and} 9.0 ± 19 \text{mmol/l})\) 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 SAI on HbA1c were not assessed in this study.

In conclusion, our data suggest that mixing glargine with SAI 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.**

<table>
<thead>
<tr>
<th></th>
<th>Basal</th>
<th>Mixed</th>
<th>Separate</th>
<th>(P)</th>
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</thead>
<tbody>
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<td>Hypoglycemia</td>
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<td>20 ± 14</td>
<td>10 ± 9</td>
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<td>47 ± 20</td>
<td>145 ± 37</td>
<td>NS</td>
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<tr>
<td>Euglycemia</td>
<td>206 ± 39</td>
<td>292 ± 21</td>
<td>205 ± 35</td>
<td>NS</td>
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Data are means ± SE.