Mixing Insulin Aspart With Detemir Does Not Affect Glucose Excursion In Children With Type 1 Diabetes Mellitus

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Running title: Mixing aspart and detemir in type 1 diabetes

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Objective: We hypothesized that insulin detemir mixed with aspart had equivalent effects on blood glucose as if being given as separate injections in pediatric type 1 diabetes mellitus.

Research Design and Methods: 14 children with type 1 diabetes were randomly assigned to either Study A (mixed insulins) or with Study B (separate insulins) for the first 10 days and crossed over for the last 10 days. Each subject underwent continuous glucose monitoring on the last 72 hours of each study.

Results: 48-hour AUC (mmol.hour/L), M-value and MAGE (mmol/L) for Study A vs. B were 457 ± 70 vs. 469 ± 112 (p = 0.58), 39.67 ± 15.37 vs. 39.75 ± 9.69 (p = 0.98), and 6.35 ± 1.92 vs. 5.98 ± 0.92 (p = 0.42), respectively.

Conclusions: Insulin detemir mixed with aspart had equivalent effects on blood glucose versus giving them as separate injections, in children with type 1 diabetes.
One of the barriers to good glycemic control in children with type 1 diabetes mellitus is multiple daily insulin injections (Martin, Licha-Muntz et al. 2002; Johns, Faulkner et al. 2008). Mixing rapid-acting and slow-acting insulin in the same syringe would decrease the number of injections and may improve adherence (Kaplan, Rodriguez et al. 2004; Fiallo-Scharer, Horner et al. 2006). Although, there are concerns that mixing the insulins would change the glucose excursion (Cengiz, Tamborlane et al.), mixing rapid-acting insulin (aspart or lispro) with slow-acting insulin glargine in the same syringe immediately before use did not change the glucose excursion and rates of hypoglycemia (Kaplan, Rodriguez et al. 2004; Fiallo-Scharer, Horner et al. 2006). We hypothesized that slow-acting insulin detemir mixed with aspart would have equivalent effects on blood glucose vs. giving them as separate injections in children with type 1 diabetes mellitus.

RESEARCH DESIGN AND METHODS

This protocol was approved by the institutional review board of the Baylor College of Medicine. The study was designed to detect a 20% difference in mean area under the curve (AUC) for blood glucose values in the 72-hour period. We assumed the \( r > 0.7 \) between repeated measures and that the standard deviation for our excursion measure AUC is approximately 30%. With these specifications and assuming a 45% dropout rate, we would require twenty subjects to achieve the final necessary sample size of eleven subjects. Eighteen pediatric subjects with type 1 diabetes mellitus (11 males and 7 females) were recruited for this 20-day, randomized, crossover, and open-labeled study. These subjects aged 14.75 ± 2.69 years and had hemoglobin \( A_1c \) (HbA1c) of 7.7 ± 0.7%. The first four subjects aged 16 yrs and higher as required by the Food and Drug Administration (FDA). The subjects were randomly assigned to either Study A (mixed insulins) or with Study B (separate insulins) for the first 10 days. They were then crossed over for the last 10 days. Each subject underwent 72-hour of continuous glucose monitoring (CGM) using CGMS® iPro™ (Medtronic, Minneapolis, MN) on the last 72 hours of Study A and B. Data of 48 hours from midnight of the first day to midnight of the third day of the 72 hour-CGM were used for analysis to ensure the same starting and ending times of monitoring for all subjects. Relative frequency of mild hypoglycemic episodes was calculated as number of glucose values between 40 and 60 mg/dL being divided by the total number of glucose values generated during the chosen 48 hours of CGM. Sustained glucose values, over times were calculated as AUC, index of blood glucose control as M-value, and glucose excursion as mean amplitude of glucose excursion (MAGE). The 48-hour M-value for each treatment of each subject was calculated using the formula: \( M = M^{BS} + M^{W} \), where \( M^{W} = (\text{Maximum blood glucose} - \text{minimum glucose})/20; M^{BS} = \text{the mean of MBSBS}; MBSBS = \text{individual M-value for each blood glucose value during the 48 hour period and was calculated as } |10 \times \log(\text{blood glucose value}/120)|^{3} \text{ as being done for 24 hour data by Schlichtkrull and colleagues (Schlichtkrull, Munck et al. 1965). The 48 hour MAGE for each treatment of each subject was calculated by modifying the method proposed by Service and colleagues (Service, Molnar et al. 1970) for CGM data as follows: Summation of} \)
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Results

Fourteen subjects completed this 20-day, randomized, crossover, open-labeled study. One male subject dropped out because of a very active sports schedule and could not continue participation. Three subjects (two males and one female) had trouble with the CGM tracing and, therefore, were excluded from the final analysis. Figure 1 shows 48-hour CGM tracing for 14 subjects. The AUC was 457 ± 70 mmol.hour/L for Study A compared to 469 ± 112 mmol.hour/L for study B (p = 0.58). The M-value was 39.67 ± 15.37 for Study A compared to 39.75 ± 9.69 for study B (p = 0.98). The MAGE was 6.35 ± 1.92 mmol/L for Study A compared to 5.98 ± 0.92 mmol/L for study B (p = 0.42). Relative frequency of mild hypoglycemic episodes was 5.3 ± 5.2% for Study A vs. 6.7 ± 11.1% for Study B (p = 0.95). There was no severe hypoglycemia in either group.

Figure 1: 48-hour CGM tracings for each subject taking detemir separately from aspart (gray) and detemir mixed with aspart (black).

Conclusions

In this study, we present data showing that insulin detemir mixed with aspart given twice daily had equivalent effects on blood glucose when compared to giving detemir and aspart as separate injections twice daily in children type 1 diabetes mellitus. There was no increase in hypoglycemia in either treatment. Further studies are needed to study long-term consequences of mixing and the effect on glycemic control.

Author contributions: TMN researched data, contributed to discussion, wrote manuscript, and review/edited manuscript. RM research data, contributed to discussion, and reviewed/edited manuscript. VSR contributed to discussion and reviewed/edited manuscript.

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REFERENCES

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