Effect of Puberty on the Pharmacodynamic and Pharmacokinetic Properties of Insulin Pump Therapy in Youth with Type 1 diabetes

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Development of biosynthetic techniques for production of human insulin enabled the pharmaceutical industry to produce rapid-acting insulin analogs that are more rapidly absorbed following subcutaneous injection than regular insulin (1-5). These analogs may be especially useful in treating adolescents with type 1 diabetes (T1DM) who require large pre-meal bolus doses due to the peripheral insulin resistance of puberty (6). When used in large doses, the peak action of regular insulin is delayed (to 3-4 hr) and the duration is markedly prolonged (to 8 hr or more) (7). The pharmacokinetic (PK) and pharmacodynamic (PD) properties of the rapid-acting insulin analogs have not been well studied in pediatric patients or when administered by continuous subcutaneous insulin infusion (CSII). This study was undertaken to examine the effect of puberty on the PK and PD of aspart insulin in pump treated patients.

Methods
21 healthy, non-obese subjects with T1DM ranging in age from 8-17 years were studied. All were receiving CSII therapy and HbA1c levels were between 6.5-8.9 %. The Yale Human Investigation Committee approved the study; written informed consent was obtained from the parents and assent from the subjects. Subjects were divided into two groups: pre-pubertal (Tanner I, n=9) and pubertal (Tanner II-V, n=12). The two groups did not differ significantly in HbA1c levels, duration of diabetes and BMI percentiles. Daily insulin doses were available in 6 prepubertal subjects (0.76 ± 0.04 unit/kg body weight/day) and 8 pubertal subjects (0.9 ± 0.06), p = 0.1.

Subjects were admitted to the Clinical Research Center on the evening prior to study. A new infusion set was placed in a gluteal location and all subjects received aspart insulin. Blood samples were obtained hourly overnight via an intravenous catheter for plasma glucose measurements and insulin doses were adjusted to achieve glucose levels between 80-120 mg/dl the next morning.

At ~8 AM the following morning baseline samples were obtained for plasma glucose and insulin. All subjects then received a 0.2 unit/kg bolus of insulin aspart and the pump was then suspended. A variable rate infusion of 20% dextrose was used to clamp the plasma glucose at 80-90 mg/dl for 5 hours (8). Glucose was measured every 5 minutes (Yellow Springs Instrument) and blood for plasma insulin was collected every 10 minutes for the first 90 minutes, then every 15-30 minutes thereafter. Insulin was measured with Mercodia Iso-Insulin ELISA, (ALPCO Diagnostics, Salem, NH). Because of sample handling problems in some of the early studies, insulin levels are reported here for only 7 subjects in each group.

Rates of exogenous glucose infusion (GIR) were analyzed over 10 minute intervals and adjusted for changes in the glucose space (8). The following parameters were determined: peak insulin levels and GIR (INS\text{max} and GIR\text{max}), insulin and GIR area under the curve (AUC\text{INS} and AUC\text{GIR}), and time to peak insulin level and GIR (Tmax\text{INS} and Tmax\text{GIR}). Data are reported as mean ± SEM. The Mann-Whitney U test was used to compare these PK/PD properties in the two groups, with 80% power to detect only large differences (1.3 S.D. apart) between groups with a two-sided significance level.
Results

Mean plasma insulin and GIR curves in the two groups of subjects are shown in the Figure. Although plasma insulin levels were slightly higher in pubertal vs. pre-pubertal subjects during the clamp, there were no significant differences in INS$_{\text{max}}$, AUC$_{\text{INS}}$, or Tmax$_{\text{INS}}$ between the 2 groups. In contrast to the similarities in PK parameters, PD responses to the same dose of insulin were increased by ~37% in pre-pubertal (mean AUC$_{\text{GIR}}$ 1326 ± 131 mg • kg$^{-1}$) versus pubertal subjects (964 ± 65, p<0.01). On the other hand, there were no significant differences between the two groups with respect to GIR$_{\text{max}}$ or Tmax$_{\text{GIR}}$.

The time delay between the peak insulin levels (Tmax$_{\text{INS}}$) and peak insulin action (Tmax$_{\text{GIR}}$) was similar in both groups: 43 ± 8 min in pre-pubertal subjects versus 41 ± 4 min in pubertal subjects, p=0.87.

Discussion

This study used the glucose clamp technique to determine the time course of action of aspart insulin in prepubertal and pubertal subjects with T1DM because this technique has become the gold standard for assessing the pharmacodynamic effects of new insulin analogs. In both groups of subjects, there was a rapid rise in plasma insulin levels, which reached peak values by ~60 minutes. INS$_{\text{max}}$ and AUC$_{\text{INS}}$ were not significantly different and the post-peak decline in plasma insulin was virtually identical in the two groups of subjects, indicating that puberty did not alter the PK properties of aspart insulin. Our results for Tmax$_{\text{INS}}$ are similar to those observed by Heinemann, et al. and Mudaliar, et al. who administered the same 0.2 unit/kg dose of aspart subcutaneously to healthy, non-diabetic adults (2,9).

The time course of insulin action, as reflected by the GIR curves, also did not differ between pubertal and pre-pubertal subjects. The most striking difference between the two groups was in the ability of the insulin bolus to stimulate glucose metabolism, as reflected by a ~37% increase in mean AUC$_{\text{GIR}}$ in the pre-pubertal versus pubertal subjects. Previous studies that utilized the euglycemic-hyperinsulinemic clamp technique demonstrated that, even in non-diabetic children, the hormonal changes of puberty are associated with a reduction in insulin responsiveness that was similar in magnitude to the differences in AUC$_{\text{GIR}}$ observed in this study (6,7,10).

Although peak plasma insulin concentrations were observed at ~60 minutes, there was an additional ~40 min delay in the time from INS$_{\text{max}}$ to GIR$_{\text{max}}$ in both groups. This delay in peak action underscores the importance of giving pre-meal bolus doses of insulin 10-15 minutes before, rather than after a meal in order to limit post-prandial glucose excursions. They also provide experimental evidence that supports the clinical utility of “residual insulin” functions of the newer insulin pumps that are designed to discourage stacking of multiple correction doses after a meal bolus and suggest waiting 3-4 hours for further correcting for elevated glucose levels.
References:

1. Howey, DC, Bowsher RR, Brunelle RL, Woodworth JR. [Lys(B28), Pro(B29)]
   human insulin: a rapidly absorbed analogue of human insulin. *Diabetes*

   acting analog of human insulin: absorption kinetics and action profile compared
   with regular human insulin in healthy nondiabetic subjects. *Diabetes Care*

   and pharmacokinetic profiles of insulin glulisine-a novel, rapid-acting, human

4. Becker RHA, Frick AD, Kapitza C, Heise T, Rave K: Pharmacodynamics (PD) and
   pharmacokinetics (PK) of insulin glulisine (GLU) versus insulin lispro (IL) and
   regular human insulin (RHI) in patients with type 2 diabetes. *Diabetes* 53

5. Danne T, Becker RHA, Heise T, Bittner C, Frick AD, Rave K: Pharmacokinetics,
   Prandial Glucose Control, and Safety of Insulin Glulisine in Children and

6. Amiel SA, Sherwin RS, Simonson DC, Lauritano AA, Tamborlane WV. Impaired
   insulin action in puberty: a contributing factor to poor glycemic control in

   Insulin resistance of puberty: a defect restricted to peripheral glucose metabolism.

8. DeFronzo RA, Tobin JD, Andres R. Glucose clamp technique: a method for
   quantifying insulin secretion and resistance. *Am. J. Physiol.* 1979; 237(3): E214-
   E223.

   Metabolic Effect of Soluble Insulin and the Rapid-Acting Insulin Analog Insulin

Figure: Pharmacokinetic and Pharmacodynamic Profiles. IA: Plasma insulin concentrations after standard bolus of 0.2 unit/kg insulin aspart in prepubertal (black square) and pubertal (white triangle) subjects. IB: Insulin action, expressed as glucose infusion rate (GIR) required to maintain euglycemia after standard bolus of 0.2 unit/kg insulin aspart in prepubertal (black square) and pubertal (white triangle) subjects. Data presented as mean ± S.E.M.