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

KARENA L. SWAN, MD[1]
STUART A. WEINZIMER, MD[1]
JAMES D. DZIURA, PHD[2]
GARRY M. STEIL, PHD[3]
GAYANE R. VOSKANYAN, PHD[3]
AMY T. STEFFEN[1]
MELODY L. MARTIN[1]
WILLIAM V. TAMBORLANE, MD[1,2]

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 who require large premeal 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 h) and the duration markedly prolonged (to 8 h or more) (7). The pharmacokinetic and pharmacodynamic properties of the rapid-acting insulin analogs have not been well studied in pediatric patients or when administered by continuous subcutaneous insulin infusion. This study was undertaken to examine the effect of puberty on the pharmacokinetics and -dynamics of aspart insulin in pump-treated patients.

RESEARCH DESIGN AND METHODS

— A total of 21 healthy nonobese subjects with type 1 diabetes ranging in age from 8 to 17 years were studied. All were receiving continuous subcutaneous insulin infusion therapy and had A1C levels between 6.5 and 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: prepubertal (Tanner stage I, $n = 9$) and pubertal (Tanner stages II–V, $n = 12$). The two groups did not differ significantly in A1C levels, duration of diabetes, and BMI percentiles. Daily insulin doses were available in six prepubertal subjects (0.76 ± 0.04 unit · kg body wt^{-1} · day^{-1}) and eight pubertal subjects (0.9 ± 0.06; $P = 0.1$).

Subjects were admitted to the clinical research center on the evening before 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 and 120 mg/dl the next morning.

At ~8:00 A.M. the following morning, baseline samples were obtained for plasma glucose and insulin. All subjects then received a 0.2 units/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 h (8). Glucose was measured every 5 min (Yellow Springs Instrument), and blood for plasma insulin was collected every 10 min for the first 90 min and then every 15–30 min 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 seven subjects in each group.

Exogenous glucose infusion rates (GIRs) were analyzed over 10-min intervals and adjusted for changes in the glucose space (8). The following parameters were determined: peak insulin levels and GIR (INS_{max} and GIR_{max}), insulin and GIR area under the curve (AUC_{INS} and AUC_{GIR}), and time to peak insulin level and GIR ($Tmax_{INS}$ and $Tmax_{GIR}$). Data are reported as means ± SEM. The Mann-Whitney *U* test was used to compare these pharmacokinetic/pharmacodynamic properties in the two groups, with 80% power to detect only large differences (1.3 SD 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 Fig. 1. Although plasma insulin levels were slightly higher in pubertal than prepubertal subjects during the clamp, there were no significant differences in INS_{max}, AUC_{INS}, or $Tmax_{INS}$ between the two groups. In contrast to the similarities in pharmacokinetic parameters, pharmacodynamic responses to the same dose of insulin were increased by ~37% in prepubertal (mean AUC_{GIR} 1,326 ± 131 mg/kg) versus pubertal (964 ± 65; $P < 0.01$) subjects. On the other hand, there were no significant differences between the two groups with respect to GIR_{max} or $Tmax_{GIR}$.

The time delay between the peak insulin levels ($Tmax_{INS}$) and peak insulin action ($Tmax_{GIR}$) was similar in both groups: 43 ± 8 min in prepubertal sub-

From the [1]Section of Pediatric Endocrinology, Yale University, New Haven, Connecticut; the [2]Center for Clinical Investigation, Yale University, New Haven, Connecticut; and [3]Medtronic MiniMed, Northridge, California.

Address correspondence and reprint requests to Karen Swan, MD, Yale University, Section of Pediatric Endocrinology, 333 Cedar St., P.O. Box 208064, New Haven, CT 06520. E-mail: karena.swan@yale.edu.

Received for publication 16 April 2007 and accepted in revised form 28 September 2007.

Published ahead of print at http//:care.diabetesjournals.org on 1 October 2007. DOI: 10.2337/dc07-0737.

S.A.W. has received honoraria for speaking engagements from Eli Lilly. W.V.T. has received honoraria for membership on an advisory board and for speaking engagements from Novo Nordisk.

Abbreviations: GIR, glucose infusion rate.

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

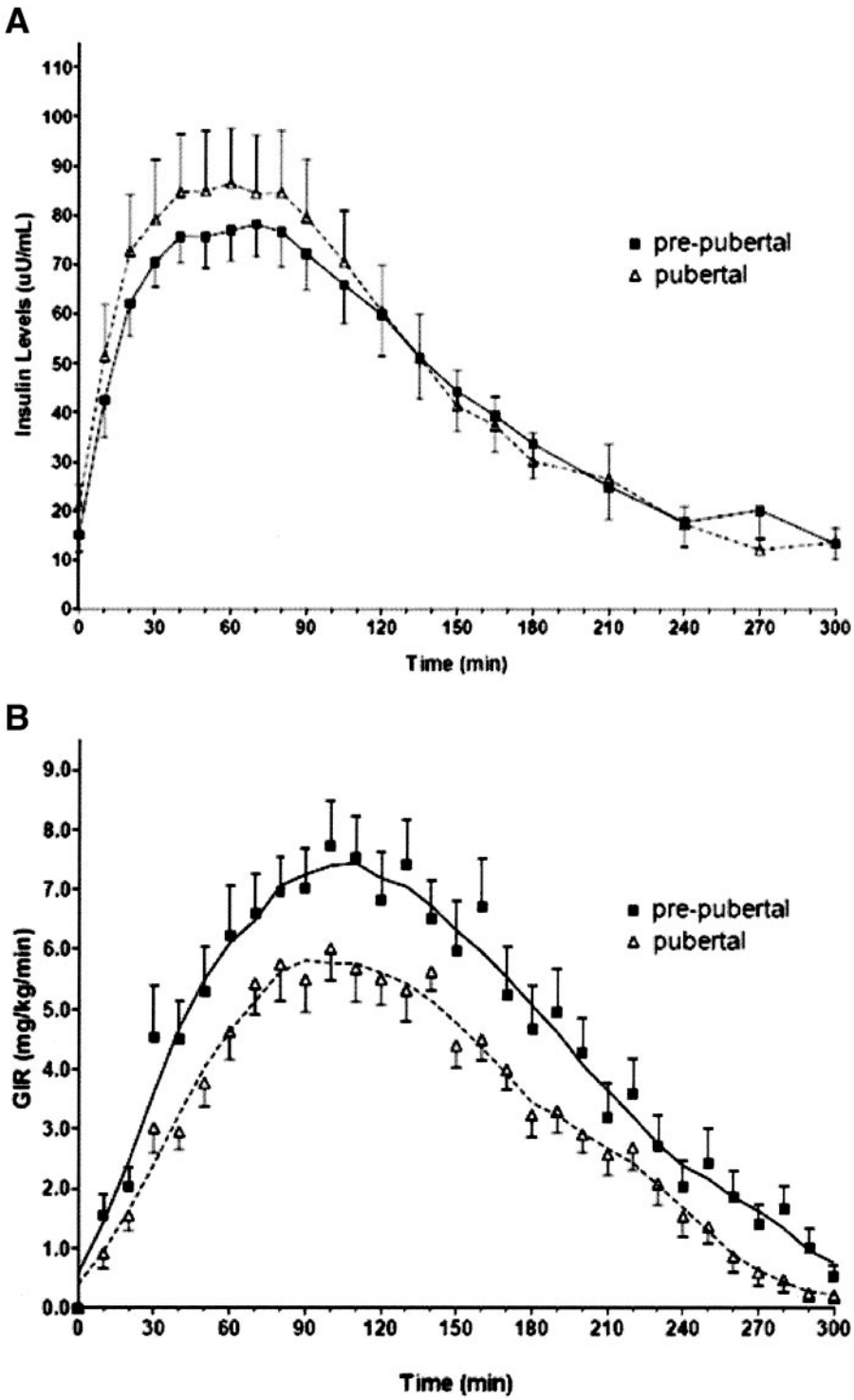

Figure 1—*Pharmacokinetic and pharmacodynamic profiles. A: Plasma insulin concentrations after standard bolus of 0.2 units/kg insulin aspart in prepubertal and pubertal subjects. B: Insulin action, expressed as GIR required to maintain euglycemia after standard bolus of 0.2 units/kg insulin aspart in prepubertal and pubertal subjects. Data presented as mean ± SEM.*

jects vs. 41 ± 4 min in pubertal subjects, $P = 0.87$.

CONCLUSIONS — This study used the glucose clamp technique to determine the time course of action of aspart insulin in prepubertal and pubertal subjects with type 1 diabetes 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 min. INS_{max} and AUC_{INS} were not significantly different, and the postpeak decline in plasma insulin was virtually identical in the two groups of subjects, indicating that puberty did not alter the pharmacokinetic properties of aspart insulin. Our results for $Tmax_{INS}$ are similar to those observed by Mudaliar et al. (2) and Heinemann et al. (9), who administered the same 0.2 units/kg dose of aspart subcutaneously to healthy nondiabetic adults.

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

Although peak plasma insulin concentrations were observed at ~60 min, there was an additional approximate 40-min delay in the time from INS_{max} to GIR_{max} in both groups. This delay in peak action underscores the importance of giving premeal bolus doses of insulin 10–15 min before rather than after a meal in order to limit postprandial 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 h 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* 43:396–402, 1994
2. Mudaliar S, Lindberg FA, Joyce M, Beerdsen P, Strange P, Lin A, Henry RR: Insulin aspart (B28 Asp-insulin): a fast-acting analog of human insulin: absorption kinetics and action profile compared with regular human insulin in healthy nondiabetic subjects. *Diabetes Care* 22:1501–1506, 1999

3. Becker RHA, Frick A, Wessels D, Scholtz H: Evaluation of the pharmacodynamic and pharmacokinetic profiles of insulin glulisine-a novel, rapid-acting, human insulin analogue (Abstract). *Diabetologia* 46: 775, 2003
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 (Abstract). *Diabetes* 53 (Suppl. 2):A119, 2004
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 adolescents with type 1 diabetes. *Diabetes Care* 28: 2100–2105, 2005
6. Amiel SA, Sherwin RS, Simonson DC, Lauritano AA, Tamborlane WV: Impaired insulin action in puberty: a contributing factor to poor glycemic control in adolescents with diabetes. *N Engl J Med* 315: 215–219, 1986
7. Amiel SA, Caprio S, Sherwin RS, Plewe G, Haymond MW, Tamborlane WV: Insulin resistance of puberty: a defect restricted to peripheral glucose metabolism. *J Clin Endocrinol Metab* 72:277–282, 1991
8. DeFronzo RA, Tobin JD, Andres R: Glucose clamp technique: a method for quantifying insulin secretion and resistance. *Am J Physiol* 237:E214–E223, 1979
9. Heinemann L, Weyer C, Rauhaus M, Heinrichs S, Heise T: Variability of the metabolic effect of soluble insulin and the rapid-acting insulin analog insulin aspart. *Diabetes Care* 21:1910–1914, 1998
10. Bloch CA, Clemmons P, Sperling MA: Puberty reduces insulin sensitivity. *J Pediatr* 110:481–487, 1987