

# Comparison of Insulin Aspart With Buffered Regular Insulin and Insulin Lispro in Continuous Subcutaneous Insulin Infusion

A randomized study in type 1 diabetes

BRUCE BODE, MD<sup>1</sup>  
RICHARD WEINSTEIN, MD<sup>2</sup>  
DAVID BELL, MD<sup>3</sup>  
JANET MCGILL, MD<sup>4</sup>  
DANIEL NADEAU, MD<sup>5</sup>

PHILIP RASKIN, MD<sup>6</sup>  
JAIME DAVIDSON, MD<sup>7</sup>  
ROBERT HENRY, MD<sup>8</sup>  
WON-CHIN HUANG, PHD<sup>9</sup>  
RICKEY R. REINHARDT, MD, PHD<sup>9</sup>

**OBJECTIVE** — To compare the safety and efficacy of insulin aspart (IAsp), buffered regular insulin (BR), and insulin lispro administered by continuous subcutaneous insulin infusion (CSII) in patients with type 1 diabetes.

**RESEARCH DESIGN AND METHODS** — After completing a 4-week run-in period with BR, 146 adult patients with type 1 diabetes (with pretrial CSII experience) were randomly assigned (2:2:1) to CSII treatment with IAsp, BR, or lispro for 16 weeks in a multicenter, open-label, randomized, parallel-group study. Bolus insulin doses were administered 30 min before meals (BR) or immediately before meals (IAsp or lispro).

**RESULTS** — Treatment groups had similar baseline HbA<sub>1c</sub> (7.3% ± 0.7 for IAsp, 7.5% ± 0.8 for BR, and 7.3% ± 0.7 for lispro). After 16 weeks of treatment, HbA<sub>1c</sub> values were relatively unchanged from baseline, and the mean changes in baseline HbA<sub>1c</sub> values were not significantly different between the three groups (0.00 ± 0.51, 0.15 ± 0.63, and 0.18 ± 0.84 for the IAsp, BR, and lispro groups, respectively). The rates of hypoglycemic episodes (blood glucose <50 mg/dl) per patient per month were similar (3.7, 4.8, and 4.4 for the IAsp, BR, and lispro groups, respectively). Clogs/blockages in pumps or infusion sets were infrequent; most subjects (76, 83, and 75% in the IAsp, BR, and lispro groups, respectively) had ≤1 clog or blockage per 4 weeks during the trial.

**CONCLUSIONS** — Insulin aspart in CSII was as efficacious and well tolerated as BR and lispro and is a suitable insulin for continuous subcutaneous insulin infusion using external pumps.

*Diabetes Care* 25:439–444, 2002

From <sup>1</sup>Atlanta Diabetes Associates, Atlanta, Georgia; <sup>2</sup>Diablo Clinical Research, Walnut Creek, California; <sup>3</sup>Kirklin Clinic, Birmingham, Alabama; <sup>4</sup>Washington University, St. Louis, Missouri; <sup>5</sup>Eastern Maine Medical Center, Bangor, Maine; <sup>6</sup>Southwestern Medical Center, Dallas, Texas; <sup>7</sup>Endocrine & Diabetes Associates, Dallas, Texas; <sup>8</sup>VA Medical Center, San Diego, CA; and <sup>9</sup>Novo Nordisk Pharmaceuticals, Princeton, New Jersey.

Address correspondence and reprint requests to Bruce W. Bode, MD, Atlanta Diabetes Associates, 77 Collier Rd. NW, Suite 2080, Atlanta, GA 30309. E-mail: bbode001@aol.com.

Received for publication 18 June 2001 and accepted in revised form 21 September 2001.

B.B. and J.M. has received honoraria from Novo Nordisk Pharmaceuticals. D.N. has received honoraria from Minimed. P.R. has received consultantships and/or is on the speaker's board for Asta Medica, Aventis, Bayer, Bristol Myers Squibb, Eli Lilly, Merck, Novo Nordisk, Pfizer, Sanwa, SmithKline Beecham, Takeda America, and Therasense and holds stock options in Therasense. J.A.D. has received consultantships and/or is on the speaker's board for Bayer Pharmaceuticals, Bristol Myers Squibb, Eli Lilly, Merck, BioControl Technologies, Pfizer, Novo Nordisk, Dura Pharmaceuticals, SmithKline Beecham, and Takeda. R.H. is a paid consultant for Novo Nordisk.

**Abbreviations:** BG, blood glucose; BR, buffered regular insulin; CSII, continuous subcutaneous insulin infusion; DCCT, Diabetes Control and Complications Trial; IAsp, insulin aspart; MDI, multiple daily injection; SD, standard deviation.

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

Continuous subcutaneous insulin infusion (CSII) therapy offers the potential of controlled basal insulin release, which can closely mimic the insulin profile of individuals without diabetes. In the Diabetes Control and Complications Trial (DCCT), patients on intensive insulin therapy could choose between CSII therapy and multiple daily injection (MDI) therapy and could change between therapies during the trial (1). Although the DCCT was not specifically designed to compare CSII and MDI therapies, the mean HbA<sub>1c</sub> value of subjects choosing CSII therapy for ≥90% of the time was 0.2% less than the HbA<sub>1c</sub> value of the MDI therapy group (2). CSII therapy has also been shown to decrease the incidence of severe hypoglycemia as compared with MDI therapy; this benefit was attributed to the greater reproducibility and flexibility of insulin administration during CSII therapy (3). These advantages of CSII, as well as improvements in pump technology, have led to increasing acceptance of insulin pump therapy (4).

Insulin aspart (IAsp) has properties that are expected to be optimal for use in CSII: soluble, rapid-acting, and uniform absorption characteristics (5). Such properties should reduce the size of the subcutaneous insulin depot and reduce the time interval between insulin administration and insulin action. Because the concept of CSII is predicated on an immediacy of insulin action, a rapid-acting insulin analog should be ideal. Studies using such an analog, lispro, have validated this concept (6,7). As currently formulated, IAsp is physically compatible for use in pumps and has been shown to be as safe and effective as buffered regular insulin (BR) in CSII therapy (8). The only insulin currently approved for CSII use in the U.S. is BR, although insulin lispro is commonly used in CSII. The present

study was conducted to further examine the suitability of IAsp for CSII therapy by directly comparing its safety and efficacy in type 1 diabetes with that of BR and lispro.

## RESEARCH DESIGN AND METHODS

— This was an open-label, randomized, parallel-group study conducted at 13 sites in the U.S. Patients with type 1 diabetes received IAsp, BR, or lispro as a continuous subcutaneous infusion by an external pump for 16 weeks. The study was performed in accordance with the Declaration of Helsinki and with the approval of local independent review boards. Written informed consent was obtained from all subjects.

### Subjects

The study enrolled 146 men and women, aged 18–71 years, who had type 1 diabetes for at least 12 months (fasting C-peptide  $<0.5$  ng/ml) and had been treated with CSII therapy continuously for the previous 3 months. In these patients, baseline BMI was  $\leq 35.0$  kg/m<sup>2</sup> and baseline HbA<sub>1c</sub> ranged from 5.7 to 9.7%. Subjects were excluded from entering the trial if they had impaired hepatic function (liver enzyme values twice the upper limit of normal), impaired renal function (serum creatinine  $>2.0$  mg/dl), impaired cardiac function, or recurrent major hypoglycemia. Women were excluded if they were pregnant, breast-feeding, or not using contraception.

### Treatments

Subjects eligible for the trial underwent a 4-week, open-label, run-in period during which all subjects used BR (Velosulin; Novo Nordisk, Bagsvaerd, Denmark). Subjects were instructed to administer bolus doses of BR 30 min before the start of each meal using their own insulin pumps: MiniMed 506 or 507 pumps (Sylmar, CA) or Disetronic pumps (Minneapolis, MN). Subjects were instructed to replace the infusion sets and the insulin at intervals not exceeding 48 h for the duration of the study. All subjects were given a One-Touch meter (LifeScan, Milpitas, CA) to measure blood glucose levels.

After the run-in period, subjects were randomly assigned (2:2:1) to the lowest available randomization number, to receive either IAsp, BR, or lispro (Humalog; Eli Lilly, Indianapolis, IN). The randomization code was provided by Novo Nor-

disk A/S (Bagsvaerd, Denmark) to ensure that the investigator and subject were blinded at the point of randomization. Subjects assigned to the IAsp or lispro groups were instructed to take bolus doses just before the start of each meal, whereas those assigned to the BR treatment group were instructed to take bolus doses 30 min before the start of each meal. During the run-in period and during the first 4 weeks after randomization (dose-adjustment period), the investigator reviewed the blood glucose meter readings with the subject to maximize drug therapy to achieve the targeted fasting (pre-breakfast) blood glucose level between 80 and 120 mg/dl without unacceptable hypoglycemia.

Subjects were contacted at least weekly during the run-in period and every 2 weeks during the dose-adjustment period. Telephone contact with the clinic could be made by the subjects in the event of problems with the treatment or by the investigator if insulin doses were modified. The subjects continued on the adjusted dose regimen during weeks 4–16 (maintenance period) unless further dose adjustment was required.

### Efficacy assessments

Efficacy was assessed by measuring HbA<sub>1c</sub> values and eight-point blood glucose (BG) levels before and 90 min after each of three meals, at bedtime, and at 2:00 A.M. The HbA<sub>1c</sub> level was determined from blood samples taken at baseline and week 16 by a central laboratory (Quest Diagnostics, San Capistrano, CA) using an assay that had linearity over the range 4.3–20.4% and a range of 4.3–6.1% for nondiabetic subjects (9,10). The eight-point BG profiles were recorded in a diary by the subject on two consecutive days during the last week of the run-in period and on two consecutive days the week before the week 16 study visit. Efficacy assessments also included changes in body weight and lipid profile (HDL, LDL, cholesterol, and triglycerides). Total daily insulin doses (adjusted by baseline body weight) for the week before baseline and the last week of treatment were determined and separated into daily basal insulin dose and daily bolus insulin dose.

### Safety assessments

Safety was assessed based on the recording of adverse events, physical examination findings, and clinical laboratory

evaluations. Subjects were asked to record hypoglycemic symptoms in their diaries, along with time of day and the BG measurements associated with those symptoms. Hypoglycemia was defined as minor when the subject had a symptom of hypoglycemia (i.e., palpitations, tiredness, sweating, strong hunger, dizziness, tremor, etc.) confirmed by BG meter reading  $<50$  mg/dl and was able to deal with the episode on their own. A hypoglycemic episode was defined as major if the BG meter reading was  $<50$  mg/dl and the event was associated with severe central nervous system dysfunction that either prevented the subject from treating himself/herself or required administration of parenteral glucose or glucagon.

Subjects were made aware of the possibility of clogs or blockages of the pump or infusion set and were told to record these events in their diaries.

### Statistical analysis

Between-treatment comparisons for all efficacy end points, except for daily insulin, were made using an ANCOVA model with treatment and center as fixed effects and the corresponding baseline measurement as the covariate. Baseline parameters were from week 0 (randomization visit); 95% CIs for the between-treatment differences in HbA<sub>1c</sub>, glucose variability, lipid profile parameters, and weight were also constructed based on the ANCOVA model. The last observation carried forward (LOCF) approach was used in the statistical analyses of HbA<sub>1c</sub>, weight, and lipid profile. Results are stated as mean  $\pm$  SEM adjusted for baseline values and center effect, as mean treatment difference (95% CI), or as indicated.

## RESULTS

### Subjects

Baseline demographic characteristics were similar for all treatment groups (Table 1). Overall, 93, 85, and 96% of the subjects receiving IAsp, BR, and lispro, respectively, completed the 16-week study.

Subjects had a mean baseline insulin requirement of 0.7, 0.6, and 0.5 units/kg in the IAsp, BR, and lispro groups, respectively, which did not change by the end of the study (Table 1). In general, subjects maintained the same insulin dose (basal and bolus) throughout the study.

Table 1—Baseline demographic characteristics and subject enrollment and attrition

	IAsp	BR	Lispro
Number of subjects treated	59	59	28
Age (years)	42.3 ± 12.0	43.1 ± 9.4	39.9 ± 11.1
Sex (male/female)	23 (39)/36 (61)	19 (32)/40 (68)	9 (32)/19 (68)
BMI (kg/m <sup>2</sup> )	26.7 ± 3.8	25.9 ± 3.8	26.3 ± 3.2
Race (Caucasians)	58 (98)	58 (98)	26 (93)
HbA <sub>1c</sub> (%)	7.3 ± 0.7	7.5 ± 0.8	7.3 ± 0.7
Insulin dose (units/kg)			
Total	0.7 ± 0.76	0.6 ± 0.18	0.5 ± 0.19
Bolus	0.4 ± 0.57	0.3 ± 0.13	0.2 ± 0.14
Basal	0.3 ± 0.23	0.3 ± 0.13	0.3 ± 0.11
Completed study	55 (93)	50 (85)	27 (96)
Total withdrawn*	4 (7)	9 (15)	1 (4)
Adverse event	1† (2)	0	0

\*Data are means ± SD or n (%). \*Withdrawal reasons include withdrawal of consent, lack of compliance, lost to follow-up, ineffective therapy, and adverse event; †subject had herpes zoster.

### Efficacy

Most subjects entered the study with relatively good glycemic control, as demonstrated by mean baseline HbA<sub>1c</sub> values <7.5%, and maintained good glycemic control throughout the study. After 16 weeks of treatment, HbA<sub>1c</sub> values were relatively unchanged from baseline and the mean changes in baseline HbA<sub>1c</sub> values were not significantly different among the three groups (0.00 ± 0.51%, 0.15 ± 0.63%, and 0.18 ± 0.84% for the IAsp, BR, and lispro groups, respectively).

Mean eight-point BG profiles at baseline and at end of study are presented in Fig. 1. Postprandial values for subjects in the rapid-acting insulin analog groups were improved from baseline values and tended to be lower than those for subjects in the BR group. A few statistically significant differences were observed at week 16 between the treatment groups: i.e., at dinner + 90 min, the BG value for the IAsp group was lower than those for BR and lispro groups ( $P = 0.019$ ); at 2:00 A.M., the BG value for the BR group was lower than those for IAsp and lispro groups ( $P = 0.002$ ).

The mean values for HDL, LDL, cholesterol, and triglycerides were within their normal limits at baseline and at week 16 for each treatment group. Mean changes in baseline values for lipid parameters were not significantly different between treatment groups. Similarly, mean weights at baseline were comparable for each group and did not significantly increase or decrease during the study.

### Hypoglycemia

Similar numbers of subjects (≥90%) in each treatment group reported one or more minor hypoglycemic episodes during the 16-week treatment period. Only one subject (in BR group) reported a major hypoglycemic episode (required intravenous glucose) during the study. Approximately one half of the hypoglycemic episodes were confirmed by a blood glucose value <50 mg/dl (Table 2). The rates and numbers of episodes of BG-confirmed hypoglycemic episodes were not significantly different between treatment groups, although there was a trend for slightly lower rates and numbers of episodes in the IAsp treatment group (Table 2). Hypoglycemic episodes reported by symptoms, but not necessarily confirmed by BG <50 mg/dl, showed that subjects in the IAsp group reported a significantly lower rate of episodes than subjects in either the BR or the lispro groups (Table 2).

Of the confirmed episodes, the rate of nocturnal hypoglycemic episodes (midnight to 6:00 A.M.) for the IAsp group was lower than that for the BR group and similar to that of the lispro group (Table 2). During the 3-month maintenance period, a greater percentage of patients in the IAsp group (41%, 24/59) were free of nocturnal hypoglycemic episodes compared with patients in the BR (20%, 12/59) or lispro (25%, 7/28) groups. No major nocturnal hypoglycemic episodes occurred during the study.

### Safety

The adverse event profiles for the three treatment groups were similar. Adverse events were reported by ~70% of the subjects; most were mild in severity. Only one subject withdrew from the trial because of an adverse event (IAsp group: herpes zoster).

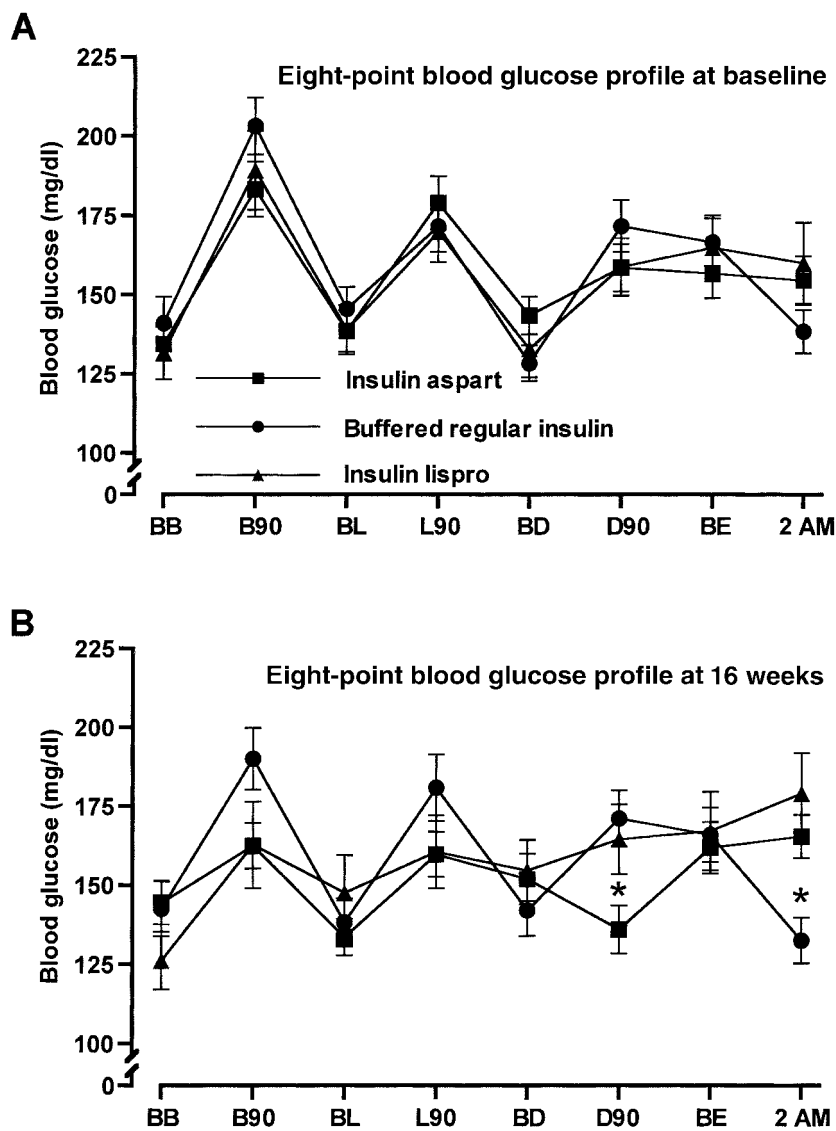
Hyperglycemia (BG >350 mg/dl) was the most commonly reported adverse event for each treatment group and was reported by 27% (16/59) of the subjects in the IAsp group, 41% (24/59) of the subjects in the BR group, and 36% (10/28) of the subjects in the lispro group; between-treatment differences were not statistically significant. There were no episodes of diabetic ketoacidosis during the trial.

No clinically significant differences between treatment groups were noted for vital signs, physical parameters, results of electrocardiography, or clinical laboratory findings.

### Pump compatibility

Most subjects (75, 78, and 64% of those in the IAsp, BR, and lispro groups, respectively) reported three or fewer clogs or blockages of the pump or infusion set during the entire treatment period. Only a small percentage of clogs or blockages (9% [15/158], 7% [9/136], and 6% [5/81] for IAsp, BR, and lispro, respectively) coincided with a hyperglycemic episode.

**CONCLUSIONS**— The present study indicates that IAsp is as effective as BR and lispro when used in CSII therapy.



**Figure 1**—Comparison of the mean eight-point blood glucose profiles (mean  $\pm$  SEM) for IAsp, BR, and lispro at baseline (A) and 16 weeks (B) for the intent-to-treat population. BB, before breakfast; B90, 90 min after breakfast; BL, before lunch; L90, 90 min after lunch; BD, before dinner; D90, 90 min after dinner; BE, at bedtime. Number of patients at each time point: insulin aspart, 52–58; BR, 48–58; lispro, 24–28. \*Statistical significant ( $P < 0.05$ ) difference between treatment groups by ANCOVA with treatment and center as the fixed effect and baseline value as the covariate.

Most subjects entered into the trial with good glycemic control, as demonstrated by mean baseline HbA<sub>1c</sub> values ranging from 7.3 to 7.5%, and maintained such control over the 4 months of the trial. These findings confirm the results of an earlier 7-week study comparing IAsp and BR in CSII therapy, in which both treatments provided comparable glycemic control in patients with type 1 diabetes (8). In a CSII study reported by Zinman et al. (7), the HbA<sub>1c</sub> values for lispro-treated

subjects were significantly improved compared with those subjects treated with regular human insulin. However, subjects in that study administered bolus doses of insulin (lispro or regular human insulin) 0 to 5 min before meals; such a study design put regular human insulin at a disadvantage, because it should be given 30 min before mealtime for optimal glucose-lowering effect. Subjects in the Zinman study also had a higher mean baseline HbA<sub>1c</sub> value (8.0%) than those in

the present study (7.3–7.5%). After 3 months of treatment, the mean HbA<sub>1c</sub> value decreased to 7.66%, a value that was slightly higher than the mean baseline HbA<sub>1c</sub> values for subjects in the present study.

Subjects were safely switched from BR in the run-in period to insulin analogs during the treatment period without having to make any adjustment in insulin dose (total, bolus, or basal) for maintenance of glycemic control during this CSII trial. As seen in studies with MDI therapy, subjects in this study had higher nighttime BG values with the use of rapid-acting insulin analogs than with BR (11,12). Adjustment of the basal insulin dose may enable patients to achieve improvement in nighttime and between-meal glycemic control, which could lead to decreases in HbA<sub>1c</sub>. However, the nocturnal basal rate should be increased carefully so that the incidence of nocturnal hypoglycemia is not also increased.

The insulin analogs in this study showed an advantage over BR in terms of improved postprandial glycemic control. For eight-point BG profiles, the postprandial BG values of the IAsp group tended to be lower than those of the BR group and were similar to those of the lispro treatment group. These results are consistent with the lowered postprandial BG values of patients using insulin analogs as the mealtime bolus in MDI therapy (12–14). The impact of postprandial glycemic control on overall glycemic control was addressed in the recent American Diabetes Association position statement stating that postprandial glucose, as well as fasting plasma glucose, and mean plasma glucose, are highly correlated with HbA<sub>1c</sub> (15). However, the importance of postprandial hyperglycemia per se as a risk factor for late complications of diabetes has not been clearly established. Nevertheless, several studies in nondiabetic and type 2 diabetic subjects have shown an increased risk of mortality and myocardial infarction associated with isolated postprandial hyperglycemia (16–22).

The overall occurrence of hypoglycemic episodes with BG values  $< 50$  mg/dl was similar for the three treatment groups, although there was a trend toward a lower rate of hypoglycemia in the IAsp group compared with the BR and lispro groups (not significant). A similar finding was demonstrated in two published studies comparing lispro with hu-

Table 2—Hypoglycemic episodes

	IAsp (n = 59)		BR (n = 59)		Lispro (n = 28)	
	Episodes	Rate*	Episodes	Rate*	Episodes	Rate*
All reported hypoglycemic episodes†						
Entire trial	1,580		2,240		1,159	
Dose-adjustment period	454	7.7 ± 6.4	577	10.3 ± 8.1	287	10.3 ± 8.2
Maintenance period	1,126	6.7 ± 5.4	1,663	10.5 ± 8.9 (P = 0.034)‡	872	10.5 ± 8.1 (P = 0.044)‡
Hypoglycemic episodes with BG <50 mg/dl						
Entire trial	841		1,049		482	
Dose-adjustment period	231	3.9 ± 4.2	279	4.9 ± 4.6	123	4.4 ± 5.6
Maintenance period	610	3.7 ± 3.6	770	4.8 ± 4.2 (P = 0.175)‡	359	4.4 ± 4.7 (P = 0.841)‡
Nocturnal hypoglycemic episodes with BG <50 mg/dl§						
Entire trial	122		265		79	
Dose-adjustment period	26	0.4 ± 0.95	58	1.0 ± 1.36	15	0.5 ± 0.74
Maintenance period	96	0.5 ± 0.83	207	0.9 ± 0.97 (P = 0.004)‡	64	0.6 ± 0.61 (P = 0.189)‡

Data are n or means ± SD. \*Rate equals the mean number (± SD) of hypoglycemic episodes reported per subject per 30 days for all subjects in the treatment group; †all reported hypoglycemic episodes regardless of BG value; ‡Wilcoxon rank-sum test, relative to the rate in the IAsp group during the maintenance period; §hypoglycemic episode with BG <50 mg/dl, occurring between midnight and 6:00 A.M.

man regular insulin in CSII, in which the rate of blood glucose–confirmed hypoglycemia for the insulin analog group was slightly but not significantly lower than the rate for regular insulin group (7,23). A significantly lower rate of hypoglycemic episodes based on symptoms alone was reported for subjects in the IAsp group than for subjects in the BR or lispro groups (Table 2). Although subjects in this study are experienced with CSII and are likely to have good hypoglycemic awareness, the rates of hypoglycemia that are based on symptoms alone are subject to possible bias in an open-label study and could represent symptoms not caused by hypoglycemia.

Nocturnal hypoglycemia is particularly problematic in patients with diabetes. In the present study, the IAsp group had a significantly lower rate of nocturnal hypoglycemia compared with the BR group and a similar rate to that of the lispro group (Table 2). A trend of lower rates of nocturnal hypoglycemia with insulin analogs (IAsp and lispro) has also been shown in studies using MDI therapy (24,25).

Prolonged clogs and blockages of the pump or infusion sets can result in insufficient administration of insulin, which can potentially lead to life-threatening diabetic ketoacidosis. Crystal formation of soluble insulins can increase the chance of occlusion in pumps and infusion sets.

IAsp is a soluble insulin that has been shown to have significantly less crystal formation than BR (8). In the present study, the suitability of IAsp for pump use was similar to that of BR and lispro, as demonstrated by a low incidence of clogs and blockages for all treatment groups. Patients in this trial were experienced with CSII and were properly educated to recognize and correct any clogs and blockages. Accordingly, patients took corrective actions, such that only a small percentage of clogs and blockages (9 to 6%) coincided with hyperglycemia (BG >350 mg/dl); in no case did a hyperglycemic episode progress to diabetic ketoacidosis.

The rapid-acting nature of insulin analogs provides patients with greater flexibility of their mealtime insulin needs because the bolus can be administered immediately before meals. This greater flexibility will likely lead to improved compliance and a better quality of life for patients using CSII therapy.

In conclusion, IAsp is a safe and effective alternative to BR and lispro for patients with type 1 diabetes and is compatible with pump use in CSII therapy.

**Acknowledgments**—This study was sponsored by Novo Nordisk Pharmaceuticals, Princeton, NJ.

The insulin aspart CSII pump study group

also includes the following investigators: James Desemone (Albany, NY), Richard Guthrie (Wichita, KS), Alan Marcus (Laguna Hills, CA), Jennifer Marks (Miami, FL), Gregory Peterson (Des Moines, IA), and Jay Skyler (Miami, FL).

We thank the following individuals for technical assistance: Deborah Armstrong, Gail Baillargeon, Lauren Currier, Donna Flanders, Kelly McCulloch, Laura Plummer, Carol Racklein, Tammy Stitch, Genevieve Streimer, Suzanne Strowig, and Marianne Vetrano.

## References

1. The Diabetes Control and Complications Trial Research Group: The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 329:977–986, 1993
2. The Diabetes Control and Complications Trial Research Group: Implementation of treatment protocols in the Diabetes Control and Complications Trial. *Diabetes Care* 18:361–375, 1995
3. Bode BW, Steed RD, Davidson PC: Reduction in severe hypoglycemia with long-term continuous subcutaneous insulin infusion in type 1 diabetes. *Diabetes Care* 19:324–327, 1996
4. Reynolds RL: Reemergence of insulin pump therapy in the 1990s. *South Med J* 93:1157–1161, 2000
5. Mudaliar SR, Lindberg FA, Joyce M, Beerdson P, Strange P, Lin A, Henry R: Insulin aspart (B28 Asp-insulin): a fast-acting an-

- alog of human insulin: absorption kinetics and action profile compared with regular human insulin in healthy nondiabetic subjects. *Diabetes Care* 22:1501–1506, 1999
6. Garg SK, Andersen JH, Gerard LA, MacKenzie TA, Gottlieb PA, Jennings MK, Chase HP: Impact of insulin lispro on HbA1c values in insulin pump users. *Diabet Obesity Metab* 2:307–311, 2000
  7. Zinman B, Tildesley H, Chiasson J-L, Tsui E, Strack T: Insulin lispro in CSII: results of a double-blind crossover study. *Diabetes* 46:440–443, 1997
  8. Bode BW, Strange P: Efficacy, safety, and pump compatibility of insulin aspart used in continuous subcutaneous insulin infusion therapy in patients with type 1 diabetes. *Diabetes Care* 24:69–72, 2001
  9. *Bio-Rad Diamat Analyzer System Operations Manual*. Richmond, CA, Bio-Rad, 1993
  10. Ellis G, Diamandis EP, Giesbrecht EE, Daneman D, Allen LC: An automated high pressure liquid chromatographic assay for hemoglobin A1c. *Clin Chem* 30:1746–1752, 1984
  11. Home PD, Lindholm A, Hylleberg B, Round PM: Improved glycaemic control with insulin aspart: a multicentre randomized double-blind cross-over trial in type 1 diabetes mellitus. *Diabetes Care* 21:1904–1907, 1998
  12. Raskin P, Guthrie RA, Leiter L, Riis A, Jovanovic L: Use of insulin aspart, a fast-acting insulin analog, as the mealtime insulin in the management of patients with type 1 diabetes. *Diabetes Care* 23:583–588, 2000
  13. Andersen JH, Brunelle RL, Kooivisto VA, Trautmann ME, Vignati L, DiMarchi R, and the Multicenter Insulin Lispro Study Group: Improved mealtime treatment of diabetes mellitus using an insulin analogue. *Clin Ther* 19:62–71, 1997
  14. Jacobs MAJM, Keulen ETP, Kanc K, Casteleijn S, Scheffer P, Deville W, Heine RJ: Metabolic efficacy of preprandial administration of lys (B28), pro (B29) human insulin analog in IDDM patients. *Diabetes Care* 20:1279–1286, 1997
  15. American Diabetes Association: Consensus statement on postprandial blood glucose. *Diabetes Care* 24:775–778, 2001
  16. Hanefeld M, Fischer S, Julius U, Schulze J, Schwanebeck U, Schmechel H, Ziegelasch HJ, Lindner J: Risk factors for myocardial infarction and death in newly detected NIDDM: the Diabetes Intervention Study, 11-year follow-up. *Diabetologia* 39:1577–1583, 1996
  17. Hanefeld M, Temelkova-Kurktschiev T: The postprandial state and the risk of atherosclerosis. *Diabet Med* 14 (Suppl. 3):S6–S11, 1997
  18. Anonymous: Glucose tolerance and mortality: comparison of WHO and American Diabetes Association diagnostic criteria: the DECODE study group. *Lancet* 354:617–621, 1999
  19. Tominaga M, Eguchi H, Manaka H, Igarashi K, Kato T, Sekikawa A: Impaired glucose tolerance is a risk factor for cardiovascular disease, but not impaired fasting glucose. *Diabetes Care* 22:920–924, 1999
  20. Shaw JE, Hodge AM, de Courten M, Chitson P, Zimmet PZ: Isolated post-challenge hyperglycaemia confirmed as a risk factor for mortality. *Diabetologia* 42:1050–1054, 1999
  21. Barrett-Connor E, Ferrara A: Isolated postchallenge hyperglycemia and the risk of fatal cardiovascular disease in older women and men: the Rancho Bernardo Study. *Diabetes Care* 21:1236–1239, 1998
  22. Balkau B, Shipley M, Jarrett RJ, Pyorala K, Pyorala M, Forhan A, Eschwege E: High blood glucose concentration is a risk factor for mortality in middle-aged nondiabetic men: 20-year follow-up in the Whitehall Study, the Paris Prospective Study, and the Helsinki Policemen Study. *Diabetes Care* 21:360–367, 1998
  23. Melki V, Renard E, Lassmann-Vague V, Booivin S, Guerci B, Hanaire-Broutin H, Bringer J, Belicar P, Jeandidier N, Meyer L, Blin P, Augendre-Ferrante B, Tauber J-P: Improvement of HbA1c and blood glucose stability in IDDM patients treated with lispro insulin analog in external pumps. *Diabetes Care* 21:977–982, 1998
  24. Home PD, Lindholm A, Riis A: Insulin aspart vs. human insulin in the management of long-term blood glucose control in type 1 diabetes mellitus: a randomized controlled trial. *Diabet Med* 17:762–771, 2000
  25. Heller SR, Amiel SA, Mansell P: Effect of the fast acting-acting insulin analog lispro on the risk of nocturnal hypoglycemia during intensified insulin therapy. *Diabetes Care* 22:1607–1611, 1999