# Efficacy, Safety, and Pump Compatibility of Insulin Aspart Used in Continuous Subcutaneous Insulin Infusion Therapy in Patients With Type 1 Diabetes

BRUCE W. BODE, MD
POUL STRANGE, MD, PHD

**OBJECTIVE** — The purpose of this study was to compare the efficacy, safety, and pump compatibility of insulin aspart (a rapid-acting insulin analog) and buffered regular human insulin in patients with type 1 diabetes undergoing continuous subcutaneous insulin infusion (CSII) therapy.

**RESEARCH DESIGN AND METHODS** — This was a single-center randomized open-label study. Patients received CSII therapy with insulin aspart ($n$ = 19) or buffered regular human insulin ($n$ = 10) for 7 weeks. Bolus doses of insulin aspart were administered immediately before meals and buffered regular human insulin 30 min before meals.

**RESULTS** — Insulin aspart and buffered regular human insulin were both effective in controlling average daily blood glucose levels (8.2 ± 1.9 and 8.5 ± 2.1 mmol/l, respectively) (mean ± SD) and maintaining serum fructosamine (343 ± 25.7 and 336 ± 27.4 µmol/l) and $HbA_{1c}$ (6.9 ± 0.6 and 7.1 ± 0.6 %) levels. Possible obstructions and set leakages were infrequently reported in both groups. Similar numbers of patients experienced hypoglycemia (blood glucose <2.5 mmol/l): 14 (74%) insulin aspart patients versus 6 (60%) buffered regular human insulin patients. Patients receiving insulin aspart had fewer hypoglycemic events per patient (2.9) than those patients receiving buffered regular human insulin (6.2). There were no differences between the two insulins in the occurrence of hyperglycemic events (blood glucose >19 mmol/l) or in the number and type of adverse events.

**CONCLUSIONS** — Insulin aspart and buffered regular human insulin were effective and well tolerated and provided similar pump compatibility when used in CSII therapy.

*Diabetes Care* 24:69–72, 2001

The intent of continuous subcutaneous insulin infusion (CSII) therapy in patients with diabetes is to administer insulin in a pattern that more closely mimics the physiological insulin secretion of individuals without diabetes. Regular human insulin, both buffered and nonbuffered, is commonly used in CSII therapy. Optimally, bolus doses of regular human insulin should be administered 30 min before a meal so that peak insulin effects will coincide with postprandial blood glucose excursions (1–3). Because of the absorption kinetics of regular human insulin, taking the bolus dose too close to a meal may result in postprandial hyperglycemia, followed by hyperinsulinemia and the risk of hypoglycemia.

From the Atlanta Diabetes Associates (B.W.B.), Atlanta, Georgia; and Novo Nordisk Pharmaceuticals (P.S.), 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 9 June 2000 and accepted in revised form 19 September 2000.

B.W.B. serves on the medical advisory board of Minimed and has received honoraria for serving on speaker's bureaus for Minimed, Novo Nordisk, and Eli Lilly. P.S. holds stock in Novo Nordisk.

**Abbreviations:** CSII, continuous subcutaneous insulin infusion; MDI, multiple daily insulin injection.

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

In recent years, it has become increasingly common to use a rapid-acting insulin analog in CSII therapy. Insulin aspart is a rapid-acting insulin analog that differs from human insulin at position B28, where proline has been replaced by aspartic acid. The modification allows insulin aspart to dissociate more quickly and be more rapidly absorbed from subcutaneous tissue than regular human insulin (4,5). The onset of action occurs in ~10–20 min, maximum serum concentrations occur in ~45 min, and the duration of action is 1–3 h (6–10). When injected at mealtime in patients receiving basal regular human insulin via CSII, insulin aspart has been associated with a more rapid rise in serum-free insulin followed by reduced hyperinsulinemia compared with regular insulin (11).

The pharmacokinetics of insulin aspart suggest that it may be suitable for use in CSII therapy. In this study, we evaluated the suitability of insulin aspart for use in CSII therapy by comparing its efficacy, safety, and pump compatibility with buffered regular human insulin in patients with type 1 diabetes. Buffered regular human insulin was selected as the comparator because at the time of study, it was the only insulin formulation approved for use in CSII pumps.

## RESEARCH DESIGN AND METHODS

— This was a single-center randomized open-label study in which patients received CSII therapy with either insulin aspart or buffered regular human insulin for 7 weeks. The study was conducted in accordance with the Declaration of Helsinki, and patients gave written informed consent.

Enrolled patients were men or women with a diagnosis of type 1 diabetes (C-peptide–negative) for 2–25 years before enrollment and who had been treated continuously for the previous 3 months with CSII therapy. Patients with a history of hypoglycemia unawareness, recurrent severe hypoglycemia, or deficiency of hypoglycemic counter regulation were excluded from enrollment. Patients with a history of signif-

**Table 1—*Demographic and baseline characteristics***

| Characteristic | Insulin aspart | Buffered regular human insulin |
|---|---|---|
| *n* | 19 | 10 |
| Age (years) | 38 ± 10.4 (20–55) | 34 ± 12.5 (20–56) |
| Sex (M/F) | 13/6 | 5/5 |
| Caucasian | 19 | 10 |
| Weight (kg) | 82 ± 13.6 (60–106) | 73 ± 9.6 (54–90) |
| Height (cm) | 177 ± 9.2 (158–192) | 172 ± 8.7 (158–183) |
| BMI (kg/m$^2$) | 26 ± 2.4 (21–30) | 24 ± 2.0 (21–28) |

Data are *n* or means ± SD (range).

icant cardiovascular, renal, or retinal disease were also excluded.

At the screening visit, patients were supplied with infusion sets (Sof-set canula 42" MMT-315, reservoir 3 ml MMT-103; MiniMed, Sylamar, CA) and instructed to continue using their own infusion pump (MiniMed models 506, 507, or 507C) and their current CSII insulin (all patients were using insulin lispro, Humalog; Eli Lilly, Indianapolis, IN) until the baseline visit 2 weeks later. Eligible patients were then randomly assigned (2:1 ratio) to receive either insulin aspart or buffered regular human insulin (Velosulin BR; Novo Nordisk, Bagsvaerd, Denmark) as replacement for their current CSII insulin. Basal and bolus doses were transferred from the patient's prestudy regimen. Bolus dosing of buffered regular human insulin was administered 30 min before meals, whereas insulin aspart bolus administration was immediately before meals. Patients were instructed to replace their insulin and tubing at 48-h (maximum) intervals during the first 6 weeks of treatment and were then allowed to use the same tubing continuously for 7 days during week 7.

Study visits occurred at the end of each treatment week. During the week, patients self-monitored their blood glucose levels using a One Touch Profile glucose meter (LifeScan, Milpitas, CA) and recorded the results four times daily (before breakfast, lunch, and dinner and before bedtime) in a diary. Patients also recorded insulin dose settings, change of infusion set and/or insulin, and any possible occurrences of system obstruction or leakage.

Patients were instructed to adjust their insulin dose using a target blood glucose range of 3.9–8.3 mmol/l (70–150 mg/dl) (12,13). Bolus doses were based on premeal blood glucose values, and basal doses were based on pre-bedtime and pre-breakfast blood glucose values. Patients were also instructed to use a premeal correction (supplement) bolus to correct out-of-range values (13).

The insulin in the reservoir and distal tubing was microscopically examined by two trained observers at the weekly visits for transparency, color changes, particle or crystal formation (scale: 0 = none, 1 = minimal, 2 = moderate/many), and pH. Serum fructosamine was measured (reportable range <5–1,000 µmol/l) at baseline and at the end of treatment weeks 2, 6, and 7. $HbA_{1c}$ was measured (reportable range 4.2–20.4%, normal range <7%) at baseline and at the end of 6 weeks of treatment from whole blood samples by Quest Diagnostics (San Juan Capistrano, CA).

Safety was assessed based on physical examinations, adverse experiences, and the occurrence of hypoglycemic or hyperglycemic episodes. Patients were educated in avoiding and treating symptomatic hypoglycemia and instructed to record the number of episodes of "unexplained" hypoglycemic events (blood glucose meter reading <2.5 mmol/l [45 mg/dl] without an appropriate explanation, e.g., delaying a meal after taking a bolus dose) and hyperglycemic events (blood glucose meter reading >19 mmol/l [350 mg/dl] without an appropriate explanation, e.g., eating a meal without taking a bolus insulin dose).

Descriptive statistics (mean, SD, range, frequency counts, and relative frequency) were used to summarize the data. Between-treatment comparisons were made using either the two-sample *t* test or Wilcoxon's rank-sum test.

**RESULTS** — There were 29 patients who were enrolled and 28 patients who completed the 7 weeks of treatment. One patient in the insulin aspart group moved away and withdrew from treatment after study week 2 and was lost to follow-up. Patient demographic characteristics are shown in Table 1.

Patients entered the study with good glycemic control, and both insulin aspart and buffered regular human insulin were effective in maintaining this control throughout the study (Table 2). Serum fructosamine and $HbA_{1c}$ levels remained at or near baseline levels for both groups, although a small decrease in $HbA_{1c}$ level was observed for the insulin aspart group. Daily self-monitored blood glucose levels averaged ~8.3 mmol/l (150 mg/dl) throughout the study for patients in both groups. Average premeal blood glucose values within each group were not significantly different from the overall average daily value, indicating that both insulin formulations were effective in controlling blood glucose fluctuations during the course of the day (Table 3).

Approximately four infusion sets were used per patient per week during the first 6 weeks of treatment in both groups. Time elapsed since changing of the infusion set did not affect blood glucose control in either group, with average glucose levels remaining consistent during the 48 h between

**Table 2—*Serum fructosamine and $HbA_{1c}$ values***

| | Insulin aspart | Buffered regular human insulin |
|---|---|---|
| *n* | 19 | 10 |
| Fructosamine (µmol/l) | | |
| Baseline | 336 ± 27.5 | 335 ± 24.1 |
| Week 2 | 339 ± 28.7 | 349 ± 36.9 |
| Week 6 | 343 ± 25.7 | 336 ± 27.4 |
| Week 7 | 344 ± 38.3 | 348 ± 26.3 |
| $HbA_{1c}$ (%) | | |
| Baseline | 7.2 ± 0.8 | 7.2 ± 0.9 |
| Week 6 | 6.9 ± 0.6 | 7.1 ± 0.6 |

Data are means ± SD. Week 2: *n* = 9 for the buffered regular human insulin group; weeks 6 and 7: *n* = 18 for the insulin aspart group. $P > 0.05$ for between-treatment comparisons.

catheter tubing changes and with an ~0.2–0.4 mmol/l (4–7 mg/dl) difference between the first and second 24-h periods. Average daily glucose levels began to increase (~1–2.2 mmol/l, 20–40 mg/dl) in both groups during continuous use of the catheter tubing in treatment week 7. There were no significant differences between the groups for any blood glucose level during this period.

No patient in the insulin aspart group required a significant dose adjustment when being transferred to insulin aspart, and average daily basal or bolus insulin doses did not significantly change during the study for patients in either group. Mean bolus doses at weeks 1 and 6 were 23 ± 6.0 and 22 ± 6.6, respectively, for the insulin aspart group and 21 ± 8.0 and 21 ± 7.9 for the buffered insulin group. Patients in the insulin aspart group did require a slightly higher basal dose (23 ± 6.0 at week 1 and 23 ± 5.4 at week 6) compared with patients in the buffered regular human insulin group (20 ± 8.0 at week 1 and 21 ± 6.7 at week 6). However, there were no statistically significant differences between the two groups for mean bolus, basal, and total insulin doses.

Both insulins appeared to be compatible with pump use. No color or transparency changes were noted for either insulin when the pump tubing and reservoir were examined. The average pH of the insulin in the reservoir and the distal tubing was maintained at 7.4 and 7.2, respectively, in both the insulin aspart and the buffered regular human insulin groups. Some insulin crystal formation occurred in both groups, although there was significantly ($P \leq 0.05$) less crystallization for the insulin aspart group compared with the buffered regular human insulin group in the reservoir (0.3 ± 0.3 vs. 1.1 ± 0.4) and distal tubing (0.3 ± 0.3 vs. 0.7 ± 0.4). Possible obstructions were reported by seven patients in the insulin aspart group and two patients in the buffered regular human insulin group. Set leakages were infrequent, being reported by four patients in the insulin aspart group and two patients in the buffered regular human insulin group. There were no changes in the assessments of pump compatibility associated with continuous 7-day use of the catheter tubing during week 7 in either treatment group.

Both treatments appeared to be well tolerated. There were 14 (74%) patients in the insulin aspart group and 6 (60%) patients in the buffered regular human insulin group who reported unexplained hypoglycemic events. The 14 patients in the insulin aspart group experienced fewer events (2.9 events/patient) than did the 6 patients in the buffered regular human insulin group (6.2 events/patient). Unexplained hyperglycemic events were reported by 14 (74%, 3.5 events/patient) patients in the insulin aspart group and 6 (60%, 3.0 events/patient) in the buffered regular human insulin group.

**Table 3—*Average blood glucose levels (mmol/l) at week 6***

| | Insulin aspart | Buffered regular human insulin |
|---|---|---|
| *n* | 18 | 10 |
| Time of day | | |
| Prebreakfast | 7.9 ± 2.8 | 8.0 ± 2.6 |
| Prelunch | 7.1 ± 2.1 | 8.0 ± 2.4 |
| Predinner | 8.4 ± 3.4 | 8.1 ± 2.8 |
| Bedtime | 8.2 ± 2.2 | 8.8 ± 3.7 |
| Overall | 8.2 ± 1.9 | 8.5 ± 2.1 |

Data are means ± SD of daily preprepranprandial glucose values since the week 5 study visit. Overall data are means of all preprandial glucose values since the week 5 study visit. $P > 0.05$ for between-treatment comparisons.

Adverse experiences, most commonly upper respiratory infections, were reported by six (32%) patients in the insulin aspart group and three (30%) patients in the buffered regular human insulin group. No injection site reactions were reported by patients in either group. One patient in the buffered regular human insulin group was treated in the emergency room for hypoglycemia with tonic clonic seizures occurring after strenuous physical activity (skiing). Mean values for BMI were unchanged from screening to the end of week 7 in both treatment groups. No other clinically significant changes in clinical laboratory test results or vital signs were noted for any patient.

**CONCLUSIONS** — Insulin aspart is a rapid-acting insulin analog, and its efficacy and safety in patients with type 1 diabetes receiving multiple daily insulin injection (MDI) therapy have been previously reported (14–18). The results of this study indicate that insulin aspart is also effective when used in CSII therapy.

Data from the Diabetes Control and Complications Trial and subsequent clinical studies have demonstrated the effectiveness of CSII therapy in providing sustained improvement in glycemic control (19–22). In the present study, the patients had previously been on CSII therapy and entered the study with $HbA_{1c}$ values at or near the American Diabetes Association target of 7% (23). Both treatments were effective in maintaining $HbA_{1c}$ levels, although a small decrease was observed for the insulin aspart treatment group. There was no statistical difference between the groups for this change; however, significant improvements in glycemic control compared with regular human insulin have been demonstrated in CSII studies using insulin lispro, another fast-acting analog (22,24). The relatively small number of patients in the present study may not have allowed enough statistical power to detect a significant difference between the groups.

Postprandial blood glucose levels were not specifically measured in this study; however, previously reported studies in which insulin aspart was used as the mealtime component of an MDI regimen have shown significantly improved control of postprandial blood glucose excursions with insulin aspart compared with regular human insulin (15,17,18). Improved postprandial control of blood glucose may show a similar advantage for insulin aspart in CSII compared with regular human insulin, although such studies have not yet been conducted.

The results of this study also indicate that the use of insulin aspart is compatible with the external infusion pump. Both insulins were associated with few reports of possible obstructions and leakages of the external infusion pump and tubing. Some insulin crystal formation occurred for both insulins in the reservoir and distal tubing, but significantly less so for patients using insulin aspart.

Insulin aspart–treated patients did require a slightly higher basal insulin dose than did patients treated with buffered regular human insulin. This observation is consistent with previously reported studies in which patients with type 1 diabetes receiving subcutaneous injections of insulin aspart used 7–10% higher doses of NPH

insulin compared with patients treated with regular human insulin (16,17). An increased amount of basal insulin has also been reported for insulin lispro in CSII (24). It may therefore be advisable to specifically caution patients using a rapid-acting insulin analog to maintain adequate administration rates of their basal insulin.

In this study, insulin aspart was associated with fewer unexplained hypoglycemic events per patient than buffered regular human insulin (2.9 vs. 6.2) among those patients having such events. These results may suggest a potential advantage with regard to hypoglycemia risk with insulin aspart, but additional studies are needed to further investigate this possibility. However, all patients undergoing intensive insulin therapy should be adequately cautioned about the potential for an increased risk of hypoglycemia compared with their previous therapy regimen.

Because many patients may not change their catheter tubing as often as instructed, the seventh week of this study was added to assess the effect of continuous 7-day use of the same tubing. Overall, no negative effects on glycemic control, occurrence of hypo- or hyperglycemia, or pump compatibility were observed for either group. However, serum glucose levels did begin to increase the longer the tubing was used, and patients should continue to be advised of the importance of replacing the catheter and tubing on a regular basis.

Insulin aspart and buffered regular human insulin were both effective and well tolerated and provided similar pump compatibility when used in CSII therapy. This study indicates that the efficacy and safety of the rapid-acting insulin analog insulin aspart make it suitable for use with an external pump in CSII therapy in patients with type 1 diabetes.

**References**


1. Lauritzen T, Pramming S, Deckert T, Binder C: Pharmacokinetics of continuous subcutaneous insulin infusion. *Diabetologia* 24: 326–329, 1983
2. Dimitriadis GD, Gerich JE: Importance of timing of preprandial subcutaneous insulin administration in the management of diabetes mellitus. *Diabetes Care* 6:374–377, 1983
3. Kinmonth AL, Baum JD: Timing of pre-breakfast insulin injection and postprandial metabolic control in diabetic children. *Br Med J* 280:604–606, 1980
4. Kang S, Brange J, Burch A, Volund A, Owend DR: Subcutaneous insulin absorption explained by insulin's physiochemical properties: evidence from absorption studies of soluble human insulin and insulin analogs. *Diabetes Care* 14:942–948, 1991
5. Brange J: Design of insulin analogues for meal-related therapy. *J Diabetes Complications* 7:106–112, 1993
6. Heinemann L, Kapitza C, Starke AAR, Heise T: Time-action profile of the insulin analogue B28Asp. *Diabet Med* 13:683–684, 1996
7. Home PD, Barriocanal L, Lindholm A: Comparative pharmacokinetics and pharmacodynamics of the novel rapid-acting insulin analog, insulin aspart, in healthy volunteers. *Eur J Clin Pharmacol* 55:199–203, 1999
8. Mudaliar SR, Lindberg FA, Joyce M, Beerdsen P, Strange P, Lin A, Henry R: 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
9. Mortensen HB, Lindholm A, Olsen BS, Hylleberg B: Rapid appearance and onset of action of insulin aspart in paediatric subjects with type 1 diabetes. *Eur J Pediatr* 159:483–488, 2000
10. Kang S, Brange J, Burch A, Vølund A, Owens DR: Absorption kinetics and action profiles of subcutaneously administered insulin analogs (Asp89, GluB27, AspB10, AspB28) in healthy subjects. *Diabetes Care* 14:1057–1065, 1991
11. Wiefels K, Hubinger A, Dannehl K, Gries FA: Insulinkinetic and -dynamic in diabetic patients under insulin pump therapy after injections of human insulin or the insulin analog (B28Asp). *Horm Metab Res* 27:421–424, 1995
12. Bode BW: Establishing and verifying basal rates. In *The Insulin Pump Therapy Book*. Fredrickson L, Ed. Sylmar, CA, MiniMed Technologies, 1995, p. 48–57
13. Davidson PC: Bolus and supplemental insulin. In *The Insulin Pump Therapy Book*. Fredrickson L, Ed. Sylmar, CA, MiniMed Technologies, 1995, p. 58–71
14. Lindholm A, McEven J, Riis AP: Improved postprandial glycemic control with insulin aspart: a randomized double-blind cross-over trial in type 1 diabetes mellitus. *Diabetes Care* 22:801–805, 1999
15. Home PD, Lindholm A, Hylleberg B, Round P, for the U.K. Insulin Aspart Study Group: Improved glycemic control with insulin aspart. *Diabetes Care* 21:1904–1909, 1999
16. 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
17. Home P, Lindholm A, Riis A: Improved long-term blood glucose control with insulin aspart versus human insulin in people with type 1 diabetes (Abstract). *Diabetes* 48 (Suppl. 1):A1567, 1999
18. Kang S, Creagh FM, Peters JR, Volund A, Owens DR: Comparison of subcutaneous soluble human insulin and insulin analogues (AspB9, GluB27, AspB10, AspB28) on meal-related plasma glucose excursions in type 1 diabetic subjects. *Diabetes Care* 14:571–577, 1991
19. The Diabetes Control and Complications Trial Research Group: Implementation of treatment protocols in the Diabetes Control and Complications Trial. *Diabetes Care* 18: 361–376, 1995
20. Boland EA, Grey M, Oesterle A, Fredrickson L, Tamborlane WV: Continuous subcutaneous insulin infusion: a new way to lower risk of severe hypoglycemia, improve metabolic control, and enhance coping in adolescents with type 1 diabetes. *Diabetes Care* 22:1779–1784, 1999
21. 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
22. Melki V, Hanaire-Broutin H, Bessières-Lacombe S, GEDEC Study Group, Tauber J: CSII versus MDI in IDDM patients treated with insulin lispro: results of a randomized, cross-over trial (Abstract). *Diabetologia* 42 (Suppl. 1):A17, 1999
23. American Diabetes Association: Standards of medical care for patients with diabetes mellitus (Position Statement). *Diabetes Care* 23 (Suppl. 1):S32–S42, 2000
24. Ciofetta M, Lalli C, Sindaco PD, Torlone E, Pampanelli S, Mauro L, Chiara DL, Brunetti P, Bolli GB: Contribution of postprandial versus interprandial blood glucose to $HbA_{1c}$ in type 1 diabetes on physiologic intensive therapy with lispro insulin at mealtime. *Diabetes Care* 22:795–800, 1999