Twice-Daily Mixed Regular and NPH Insulin Injections With New Jet Injector Versus Conventional Syringes: Pharmacokinetics of Insulin Absorption

JEAN-PIERRE HALLÉ, M.D., JEAN LAMBERT, Ph.D., ISTVAN LINDMAYER, KARIM MENASSA, FRANCINE COUTU, Ph.D., ALBERT MOGHRABI, D.E.C., LISE LEGENDRE, T.M.A., CLAUDINE LEGAULT, B.Sc., AND GASTON LALUMIÈRE, Ph.D.

The purpose of the present study was to evaluate the feasibility of using a jet injector in a split and mixed regular and NPH insulin regimen and to compare serum glucose and free-insulin profiles obtained with the injector and the conventional syringe and needle. Twelve insulin-dependent diabetic patients were hospitalized for 5 days. After a stabilization day, six patients received their insulin injection with the injector for 2 days and with the syringe and needle for the following 2 days; the regimen was reversed for the other six patients. Diet, exercise, and insulin dosage remained constant. The serum glucose levels with the injector were consistently lower than those obtained with the syringe at all times of the day except at 5:00 a.m. and 7:30 a.m., when mean values were similar for both treatments. Free-insulin levels were higher with the injector from 10:30 a.m. to 4:30 p.m. These findings suggest that insulin absorption is faster and possibly greater with the injector than with the syringe. When switching from a syringe to an injector insulin program, insulin dose adjustment may be necessary. DIABETES CARE 1986; 9:279–82.

In spite of many promising sophisticated approaches for a more physiologic insulin delivery,[1–8] multiple insulin injections, associated with self-monitoring of blood glucose (SMBG), remain the most widely used means to achieve this goal in insulin-dependent diabetes mellitus (IDDM).[1–5] Because of pain and psychological aversion to needles, some patients are reluctant to inject themselves several times a day. An insulin jet injector may improve patients' compliance to multiple injection protocols. With these high-pressure devices, insulin is ejected through a very fine hole (diameter: 8/1000 in.). At high velocity, the shock wave generated in front of the insulin bolus pierces the skin and the insulin spreads into the subcutaneous area without the need to use a needle.

A new insulin jet injector (Preci-Jet 50, Advanced Medical Technologies, Charlottetown, Prince Edward Island C1E 1B0, Canada) allows the mixing of two types of insulin in variable and accurate amounts. It weighs 160 g and measures 2 × 14 cm. It can be used easily by patients with severe visual impairment. Sterilization can be accomplished at home by placing the two front parts and the covering cap in boiling water for 20 min. Punch pressure is adjustable to individual skin resistance. Other characteristics and the results of technical tests are described in another article in this issue of DIABETES CARE.[9]

The present study was undertaken to compare the serum glucose and free-insulin profiles obtained with the injector to those obtained with conventional syringe and needle injections. We used a regimen of mixed regular and NPH insulin before breakfast and before dinner. This regimen was chosen because it is the most widely used in our IDDM population. It also provided the opportunity to evaluate the feasibility of mixing two types of insulin in a jet injector.

MATERIAL AND METHODS

Patient population. Twelve volunteers with IDDM were selected from the outpatient diabetes clinic at Sacré-Coeur Hospital, Montreal, and gave informed consent. Patients' ages were 24.8 ± 3.2 yr and duration of diabetes was 10.2 ± 4.6 yr. These patients were normal weight except for one (patient 10: 124% ideal weight). Mean peak C-peptide concentration after glucagon injection (1 mg i.v.) was 0.11 ± 0.13 pmol/ml (range 0.03–0.47 pmol/ml) at the time of the study. (Normals: $\bar{x}$ = 1.28, range 0.91–1.88 pmol/ml; IDDM: $\bar{x}$ = 0.34, range 0.08–0.78 pmol/ml.[10])

Protocol. The patients were hospitalized for 5 days. The amount and timing of exercise, diet, and insulin dosage remained constant for each patient throughout this period. The individual programs were established at a prehospitalization visit. On that occasion, the best "back-off" (adjustment of the injector punch pressure) for each site (arms, abdomen, thighs) was selected by testing with a saline solution. It also provided the patient with an opportunity to familiarize himself with the device.

The patients were admitted in the evening of day 0. Day 1 was considered a stabilization day (data were not included in the analysis). On days 2 and 3, six patients, randomly selected, received their insulin with the jet injector while the other six received their insulin with syringes and needles. On days 4 and 5, the patients were crossed-over and received their insulin with the alternate method.

The insulin regimen consisted of a mixture of regular and NPH insulin given 30 min before breakfast and 30 min before the evening meal. The same injection sites were used throughout the study. Each patient continued to use the species of insulin (i.e., beef and pork, pork, or human) used before entering the study in order to prevent possible change in anti-insulin antibody binding.[11-13]

Because preliminary tests suggested faster insulin absorption and lower serum glucose levels with the injector compared with a syringe, the usual insulin dosage was decreased on the first day to prevent hypoglycemia. This maneuver resulted in serum glucose levels higher than usual for these patients, but no further change in insulin dosage was made. On days 2–5, a heparinized indwelling catheter was kept in place in an antecubital vein. Blood was withdrawn before and 2 h after each meal and every 2 h from 9:00 p.m. to 7:00 a.m. for the determination of serum glucose and free-insulin levels.

Laboratory methods. Serum glucose was analyzed by the glucose-oxidase method with a KDA analyzer (American Monitor, Indianapolis, IN). The C peptide was measured by ra-

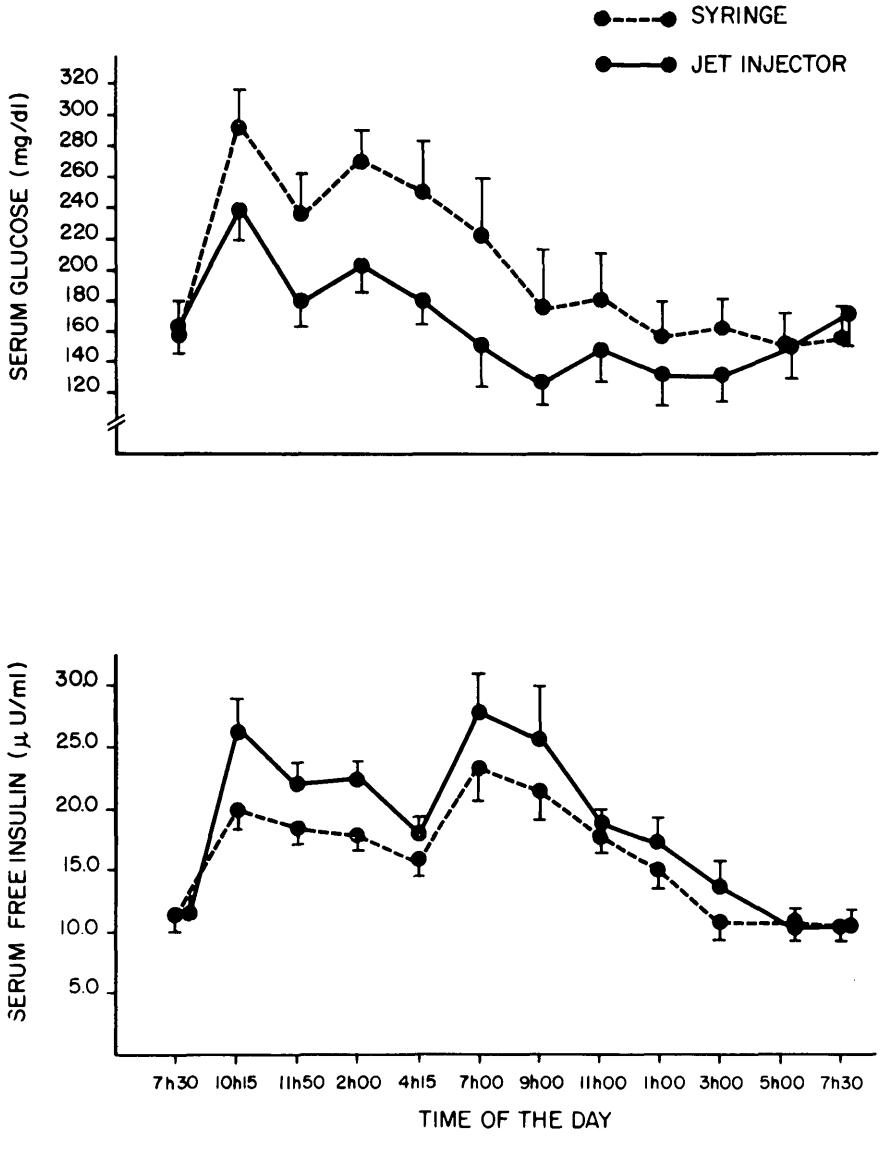

FIG. 1. Mean ± SEM serum glucose and free-insulin levels for the 2 days patients used the jet injector (●——●) vs. levels for the 2 days patients used the conventional syringes (●-----●) (N = 12).

dioimmunoassay with a kit supplied by Immunoassay Systems Malinckrodt (St. Louis, MO). According to the manufacturer, there is no cross-reactivity with insulin, glucagon, secretin, or gastric inhibitory polypeptide.

The free insulin was extracted from the serum with a polyethylene glycol solution.[14] Serum free-insulin levels were measured by radioimmunoassay with the double-antibody precipitation methods (Bio-RIA KT-1001, Montreal, Canada). Experimental conditions were modified (extract volume 200 μl; incubation time 17 h) to obtain a good sensitivity (3 μU/ml) in the lower range of the standard curve, thus enabling the detection of small increments of free-insulin levels after insulin injection.

RESULTS

As depicted in Figure 1, the mean serum glucose levels obtained with the injector were consistently lower than those obtained with a syringe, except at 5:00 a.m. and 7:30 a.m. when mean values were similar for both treatments. Between-subject variability (as represented by standard deviations and coefficients of variation) did not show any particular trend or difference between syringe and injector serum glucose levels.

A three-factor analysis of variance was performed on the serum glucose profiles. Results showed that both groups, characterized by the instrument order, were similar ($P = .290$). A preliminary analysis of variance showed no significant difference ($P = .477$) on the order effect. The between-day comparison was not significant ($P = .833$). However, results showed that injector serum glucose profiles were significantly lower ($P = .010$) than those obtained with a conventional syringe. Finally, none of the tested interactions was statistically significant. The within-patient variations in serum glucose levels were similar whichever instrument was used.

Serum free-insulin levels (Figure 1) were significantly higher ($P = .05$) with the injector than with the syringe at 10:15 a.m. and 4:15 p.m. At other times of the day, there was a general tendency for higher values with the injector. The within-patient variations were similar whichever device was used; there were no order effects and none of the tested interactions was significant.

DISCUSSION

The main objective of this trial was to compare the serum glucose and free-insulin profiles obtained with the injector and the syringe, by use of a split and mixed regular and NPH insulin regimen with both methods. The results demonstrated that the use of a jet injector for such a regimen is feasible. Consistently lower serum glucose throughout the day followed by an increase at the end of the night suggested that insulin absorption was faster with the injector. The injector induced higher free-insulin levels than the syringe from 10:15 a.m. to 7:00 p.m. This finding was not unexpected, since Taylor et al.[15] showed lower serum glucose and higher free-insulin levels 15 and 30 min after a regular insulin injection with a jet injector gun (Med-E-Jet, Med-E-Jet Corp., Cleveland, OH). However, in their study both devices gave a similar value at 60 min. From 4 to 6 h after the injection, the pattern reverted to higher serum glucose and lower free-insulin levels with the injector than with the syringe. More recently, Pehling and Gerich[16] reported similar results with the Medi-Jector (Derata, Minneapolis, MN). In our study, a faster absorption of NPH, in addition to regular insulin, may explain the prolonged hyperinsulinemia and hypoglycemic effect.

The faster insulin absorption may be more advantageous. We have the impression that, with the syringe, there is a carry-over effect because a part of the preceding day's insulin continues to be absorbed during the morning. From a theoretical point of view, this overlapping insulin effect may complicate day-to-day adjustment of insulin dosage.

More rapid insulin absorption is also desirable in protocols in which a regular insulin bolus is given before each meal. The postprandial rise of insulin levels that follows a conventional premeal regular insulin injection is slower and of longer duration than that of normal subjects. For this reason, it is difficult to really match the plasma insulin levels with the blood glucose curve. The relatively slow insulin absorption inevitably results in early hypoinsulinization (30–60 min after meals) and later overinsulinization (2–4 h after meals). In recent publications,[17,18] the best glycemic response was achieved with boluses at 60 min before the meal. The earlier injections compensated for the slow absorption and resulted in a better matching of serum insulin and glucose peaks. However, preprandial hypoglycemia was frequent and could be a major problem. Furthermore, a 60-min lag between injections and meals is not convenient for most patients. From a theoretical point of view, the faster absorption observed with the injector may allow a better matching of plasma insulin and blood glucose peaks. The present short-term study, with fixed insulin dosage, did not determine what level of diabetes control can be achieved with the use of the injector.

In conclusion, a split and mixed insulin regimen is feasible with the Preci-Jet 50. Insulin absorption is more rapid with the injector than with conventional syringes. Consequently, slight adjustments of insulin dosage are advisable when switching from the syringe to the injector. Further studies are necessary to determine which patients will derive the most benefit from this method of insulin delivery.

ACKNOWLEDGMENTS: We thank Drs. Alicia Schiffrin, Mimi M. Belmonte, and John Nasmith for reviewing the manuscript. We also thank Dr. Gilles Brisson from the Biochemistry Department, Ste.-Justine Hospital, Montreal, Canada, for the measurement of C peptide. We are grateful to Raymond Grundwald and Madeleine Arminjon from Preci-Tech for their constant collaboration. We acknowledge the work of Nurse Pauline Lavigne, the staff of the N.D.P. ward, Hélène Roussel and Jeannot Bérubé from the audiovisual department, Sacré-Coeur Hospital, Montreal. We express our gratitude to the patients who participated in the study. We are indebted to Diane L. Abastado for her skillful secretarial work.

This project was supported by the Department of Supply and Services and the Department of Veterans Affairs, Canadian Government.

From the Department of Medicine, Sacré-Coeur Hospital and Université de Montréal, Montreal, Canada.

Address reprint requests to Dr. Jean-Pierre Hallé, Chief, Division of Endocrinology, Sacré-Coeur Hospital, 5400 Gouin Blvd. West, Montreal, Québec H4J 1C5, Canada.

REFERENCES

[1] Skyler, J. S., Seigler, D. E., and Reeves, M. L.: A comparison of insulin regimens in insulin-dependent diabetes mellitus. Diabetes Care 1982; 5 (Suppl. 1):11–18.

[2] Schiffrin, A., and Belmonte, M. M.: Comparison between continuous subcutaneous insulin infusion and multiple injections of insulin. A one-year prospective study. Diabetes 1982; 31:255–64.

[3] Reeves, M. L., Seigler, D. E., Ryan, E. A., and Skyler, J. S.: Glycemic control in insulin-dependent diabetes mellitus. Comparison of out-patient intensified conventional therapy with continuous subcutaneous insulin infusion. Am. J. Med. 1982; 72:673–80.

[4] Calabrese, G., Bueti, A., Santeusanio, F., Giombolini, A., Zega, G., Angeleati, G., Cartechini, M. G., and Brunetti, P.: Continuous subcutaneous insulin infusion treatment in insulin-dependent diabetic patients: a comparison with conventional optimized treatment in a long-term study. Diabetes Care 1982; 5:457–65.

[5] Schiffrin, A., and Belmonte, M. M.: Multiple daily self-glucose monitoring: its essential role in long-term glucose control in insulin-dependent diabetic patients treated with pump and multiple subcutaneous injections. Diabetes Care 1982; 5:479–84.

[6] Hamet, P., Abarca, G., Lopez, D., Hamet, M., Bourque, M., Peyronnard, J. M., Charron, L., and Larochelle, P.: Patient self-management of continuous subcutaneous insulin infusion. Diabetes Care 1982; 5:485–91.

[7] Hanna, A. K., Minuk, H. L., Albisser, A. M., Marliss, E. B., Leibel, B. S., and Zimman, B.: A portable system for continuous intravenous insulin delivery: characteristics and results in diabetic patients. Diabetes Care 1980; 3:1–8.

[8] Schade, D. S., Eaton, R. P., Friedman, N. B., and Spencer, W. J.: Normalization of plasma insulin profiles with intraperitoneal insulin in diabetic man. Diabetologia 1980; 19:35–39.

[9] Lindmayer, I., Menassa, K., Lambert, J., Moghrabi, A., Legendre, L., Legault, C., Letendre, M., and Hallé, J.-P.: Development of a new jet injector for insulin therapy. Diabetes Care 1986; 9:294–97.

[10] Faber, O. K., and Binder, C.: C-peptide response to glucagon. A test for the residual beta-cell function in diabetes mellitus. Diabetes 1977; 26:605–10.

[11] Kurtz, A. B., Mustaffa, B. E., Daggett, P. R., and Nabarro, J. D. N.: Effect of insulin antibodies on free and total plasma insulin. Lancet 1977; 2:56–58.

[12] Asplin, C. M., Hartog, M., and Goldie, D. J.: Change of insulin dosage, circulating free and bound insulin and insulin antibodies on transferring diabetics from conventional to highly purified porcine insulin. Diabetologia 1978; 14:99–105.

[13] Fineberg, S. E., Galloway, J. A., Fineberg, N. S., and Goldman, J.: Effects of species of origin, purification levels, and formulation on insulin immunogenicity. Diabetes 1983; 32:592–99.

[14] Nakagawa, S., Nakayama, H., Sasaki, T., Yoshino, K., Yu, Y. Y., Shinozaki, K., Aoki, S., and Mashimo, K.: A simple method for the determination of serum free insulin levels in insulin-treated patients. Diabetes 1973; 22:590–600.

[15] Taylor, R., Home, P. D., and Alberti, K. G.: Plasma free insulin profiles after administration of insulin by jet and conventional syringe injection. Diabetes Care 1981; 4:377–79.

[16] Pehling, G. B., and Gerich, J. E.: Comparison of plasma insulin profiles after subcutaneous administration of insulin by jet spray and conventional needle injection in patients with insulin-dependent diabetes mellitus. Mayo Clin. Proc. 1984; 59:751–54.

[17] Dimitriadis, G. D., and Gerich, J. E.: Importance of timing of preprandial subcutaneous insulin administration in the management of diabetes mellitus. Diabetes Care 1983; 6:374–77.

[18] Kinmonth, A. L., and Baum, J. D.: Timing of pre-breakfast insulin injection and post-prandial metabolic control in diabetic children. Br. Med. J. 1980; 280:604–606.