Intravenous Insulin Infusion System to Determine Insulin Regimen in Diabetics

MASAAKI ITO, TOKUTARO SATO, TUYOSHI SAITO, MASARU KOKUBUN, MICHIKO INOUE, KAZUKO SAITO and KAORU YOSHINAGA

The Second Department of Internal Medicine, Tohoku University School of Medicine, Sendai 980

ITO, M., SATO, T., SAITO, T., KOKUBUN, M., INOUE, M., SAITO, K., and YOSHINAGA, K. *Intravenous Insulin Infusion System to Determine Insulin Regimen in Diabetics*. Tohoku J. exp. Med., 1988, **154** (1), 29-36 — An algorithm for insulin infusion system to control blood glucose was derived from results of intravenous (i.v.) insulin infusion performed on 10 diabetics. I.v. insulin infusion was done on 14 diabetics for 24 hr using the algorithm, and blood glucose was controlled within the proper range in all cases; mean blood glucose was 130 ± 42 mg/100 ml. During the examination, 4 of 14 cases did not need insulin infusion from midnight to the morning (type A) and 7 cases needed insulin infusion from midnight to the morning (type B). In 3 cases, insulin infusion was not needed at midnight, but blood glucose rose markedly in the early morning followed by insulin infusion (type C). The insulin regimen was determined according to the amount of insulin infused during the examination, dividing insulin dosages into two separate doses using semilente in the morning and a mixture of regular and lente insulin in the evening. In all the cases of type A and B, blood glucose was controlled well on the calculated regimen of insulin. However, good control of blood glucose was not obtained in 3 diabetics of type C. It is concluded that the algorithm is reliable in the estimation of the insulin infusion rate to control blood glucose in the diabetics, and the insulin regimen calculated from the result of intravenous insulin infusion is proper in about 78% of the diabetics. ——— diabetes; insulin infusion; algorithm

The determination of the doses and the kinds of insulin and the time of its injection in the treatment of diabetes mellitus is made according to the doctor's personal experience in general, taking the diurnal changes in blood glucose into consideration. The diabetics who need insulin injection are usually required to stay longer in a hospital to get a proper insulin regimen. Genuth and Martin (1977) obtained some favorable results in the control of blood glucose in the insulin dependent diabetics using an open loop control system without the feedback system of blood glucose. Lambert et al. (1978) tried to estimate the quantity of insulin in the unstable diabetics by using an artificial pancreas. However, they failed to get desired control. Their unsatisfactory result seemed to

have been caused partly by their insulin infusion algorithm, which was designed to get blood glucose stability by infusion of both insulin and glucose.

The present study was undertaken to determine if better control of diabetes mellitus can be obtained on the insulin regimen calculated from the results of intravenous insulin infusion.

PATIENTS AND METHODS

Algorithm to determine insulin infusion rate. Continuous intravenous insulin infusion was applied on 10 insulin-requiring diabetics, 6 males and 4 females, to control blood glucose. Mean age of them was 52 years, insulin doses ranged from 14 to 36 units with an average of 23.8 units per day. Mean duration of intravenous insulin infusion was 31 hr, and insulin infusion rate was changed according to the blood glucose level which was measured at 30 min intervals. We selected 148 out of 445 insulin infusion rates which were proper to control the blood glucose levels between 60 and 140 mg/100 ml. Relationship between the levels of blood glucose and the insulin infusion rate was examined. As the result, when the blood glucose level is rising, the relation between blood glucose (X) and the insulin infusion rate (Y) was represented by the regression equation; $Y = 0.03X - 2.25$ ($r = 0.74$, $p < 0.01$). When the blood glucose level is falling, the relation between them was represented by the regression equation; $Y = 0.02X - 1.48$ ($r = 0.71$, $p < 0.01$). Based on the two formulas, we made up the insulin infusion algorithm as shown in Fig. 1.

Patients. The intravenous insulin infusion was done on 14 insulin-treated diabetics who were hospitalized in our department, Nagai-City Hospital and Furukawa-City Hospital. Their sex, age, height, body weight, duration of diabetes, main complications and total calorie of diet are shown in Table 1.

Intravenous insulin infusion. A diabetic diet of 23 to 35.7 K calories per kg of ideal body weight with about 50 percent carbohydrate was prescribed. After at least a week of usual treatment, the diurnal variation of blood glucose was determined; the estimation was

TABLE 1. *Individual data*

Patient No.	Sex	Age (years)	Height (cm)	Weight (kg)	Duration of diabetes (years)
1	M	46	162	51	2
2	F	68	148	30	7
3	F	21	142	42	4
4	F	56	148	45	8
5	F	15	163	41	1
6	M	29	170	57	1
7	M	45	169	65	1
8	M	50	169	84	10
9	M	51	169	60	10
10	F	34	150	34	3
11	F	51	156	59	19
12	M	52	170	55	1
13	F	45	160	56	12
14	M	47	178	70	10

Fig. 1. Insulin infusion algorithm.

—, for blood glucose rises; ----, for blood glucose falls.

made before breakfast, 2 hr after breakfast, before lunch, 2 hr after lunch, before supper, 2 hr after supper, 9:00 p.m., 12:00 in the midnight, 3:00 a.m. and before breakfast in the second morning. After this measurement, an explanation of the examination was given to each patient, who consented.

A teflon catheter was inserted into the left forearm vein. The catheter and the tubes of infusion bottles were connected with a three-way-stopcock. The catheter and the three-way-stopcock were fixed on the arm and covered with a bandage. A Holter Pump (Model 907) or an intravenous pump (Set 9130 C, Extracorporeal Medical Specialties Inc.,

of 14 cases of diabetics

Diet (kcal/day)	Insulin dose (units)	Retinopathy	Nephropathy	Neuropathy
1300	38	—	—	—
1200	22	—	+	—
1200	30	—	—	—
1200	14	Scott IV	+	+
1700	36	—	—	—
1600	20	Scott IIa	—	—
1800	38	—	—	—
1600	24	Scott IIa	—	—
1600	30	Scott IIIa	—	—
1400	30	—	—	+
1800	40	Scott V	—	—
1800	24	—	—	—
1600	28	Scott IIa	—	—
2200	28	—	—	—

King of Prussia, PA, USA) was used. The length of the tubing between the pump and the patient's arm was 1.75 m. For the intravenous infusion, regular insulin (Iszilin, Shimizu Pharmaceutical Co., Ltd., Shimizu, 20 U/ml) was used. To avoid the absorption of insulin by the walls of the infusion apparatus, insulin was dissolved in 3.5% polygelin (Haemacel; Hoechst, Frankfurt, FRG) (Kraegen et al. 1975). Two kinds of insulin solution, 0.02 U/ml and 0.1 U/ml, were prepared. By changing the silicon tubes of the two intravenous pump sets, the infusion rates were varied from 0.2 U/hr to 4.9 U/hr. Practically, the pump and the two bottles of insulin were fixed to a stand with casters, and the infusion was carried out continuously for 24 hr.

The insulin infusion rate was determined according to our own insulin infusion algorithm (Fig. 1). The initial doses was determined on the basis of the algorithm for the rising phase of blood glucose. Afterwards the blood glucose was measured every 30 to 60 min to readjust the infusion rate according to the algorithm. When the blood glucose was same as previous result at high level, the insulin infusion rate was determined on the basis of the algorithm for the rising phase of blood glucose. For one hr after the start of each meal, the rate was fixed at 4 U/hr. An hour after the start of each meal, the patients were asked to take a walk in the hospital for 5 to 30 min; the duration of a walk was determined individually according to their habitual physical exercise and degree of complications. After 9:00 p.m., the insulin infusion rate was carefully adjusted by changing 0.1 U/hr to 0.2 U/hr every 15 to 30 min to control the blood glucose at the level of 80 to 120 mg/100 ml. When the blood glucose went down below 70 mg/100 ml, 3.5% polygelin without insulin was infused at a rate of 10 ml/hr.

Determination of insulin regimen according to the experiment. In the morning following the day of the examination, semilente insulin was injected subcutaneously in a dose corresponding to the amount of insulin required to control the blood glucose from breakfast to supper on the test day. Before supper, regular insulin and lente insulin were injected. The dose of regular insulin was determined as follows: (the amount of insulin required for 4 hr after supper) - (the average hourly dose of insulin during the night) $\times$ 4.

The dose of lente insulin, for the replacement of basal insulin requirement between supper and the next morning was calculated as follows: the amount of insulin required during the night + (the average hourly dose of insulin during the night) $\times$ 4. "The night" means the period beginning 4 hr after the supper to breakfast in the next morning. The amount of insulin to be administered was determined by every 2 U; 1 U or over was raised to 2 U, and 0.9 or lower was discarded. If the patients had insulin allergy or lipodystrophy, they received actrapid M.C. (Novo Industry A/S, Bagsvaerd, Denmark, 40 U/ml) or insulin retard Leo RI (40 U/ml; Nordisk Insulin Laboratorium, Gentofte, Denmark).

Five days after the examination, the diurnal changes of blood glucose were checked again and compared with those before the examination. Mean blood glucose (MBG) and M-value were calculated from diurnal changes of blood glucose (Schlichtkrull et al. 1965; Goto and Kikuchi 1972). The blood glucose level was measured by an autoanalyzer (Hitachi-726, Hitachi Kohki Co., Ltd., Tokyo) for diurnal change, and by Dextron/Eyetone system (Cohen et al. 1964; Jarret et al. 1970) during the examination.

RESULTS

Fig. 2 shows records of blood glucose profiles in cases 8, 12 and 14 regulated by continuous intravenous insulin infusion according to our own algorithm for 24 hr. In case 8, blood glucose was regulated well without insulin infusion during night (type A). In case 12, insulin infusion was needed during night to control blood glucose (type B). In case 14, insulin infusion was not required to maintain the levels of blood glucose at about 70 to 100 mg/100 ml during the night, after

Fig. 2. Changes of blood glucose during continuous insulin infusion.

●—●, type A; ○—○, type B; △—△, type C.

11:00 p.m. to 2:00 a.m. However, at 4:00 a.m., blood glucose rose to 190 mg/100 ml and insulin infusion was required again. Cases 10 and 13 showed quite similar blood glucose profiles during the night (type C). Number of cases of type A, B and C was 4, 7, and 3, respectively.

Table 2 shows the doses of insulin, mean blood glucose and M-value before

TABLE 2. *Changes of mean blood glucose (MBG), M-value and insulin dose after insulin infusion*

Type	MBG (mg/100 ml)		M-value		Insulin dose (U/day)	
	Before	After	Before	After	Before	After
A (n = 4)	163.0 ± 58.3	119.8 ± 17.2**	29.4 ± 29.3	11.5 ± 5.3	26.5 ± 4.1	22.5 ± 9.4
B (n = 7)	225.1 ± 76.6	124.8 ± 22.4**	67.0 ± 61.6	11.3 ± 7.1	30.0 ± 10.5	30.6 ± 6.6
C (n = 3)	204.1 ± 64.5	259.4 ± 50.6	74.5 ± 32.1	111.3 ± 23.7	28.7 ± 1.2	27.3 ± 3.1
Total (n = 14)	202.9 ± 69.9	152.2 ± 63.8**	57.9 ± 49.7	30.8 ± 43.7	28.7 ± 7.5	27.6 ± 7.4

Values are means ± S.D.

** $p < 0.01$ against values before insulin infusion.

Fig. 3. Changes of mean blood glucose and M-value by changes of insulin regimen after insulin infusion.

B, breakfast ; L, lunch ; S, supper ; E, exercise.

and after the insulin infusion. After the examination, insulin doses decreased slightly in the group of type A, and did not change in the groups of type B and C. In most cases, the blood glucose levels were controlled in the proper range by the insulin regimen calculated from the results of the examination. MBG decreased from 202.9 ± 69.9 to 152.2 ± 63.8 ($p < 0.01$). M-values also decreased from 57.9 ± 49.7 to 32.8 ± 47.6 by the calculated insulin regimen. MBG and M-value decreased markedly in the diabetics of type B, however not in the diabetics of type C. As shown in Fig. 3, both the MBG and M-value after the examination were at the proper range in all the cases of the type A and B, and were at higher range in all 3 cases of type C.

DISCUSSION

It is a disputable problem whether good control of blood glucose can prevent

angiopathy perfectly in patients with diabetes mellitus (Tchobroutsky 1978). At present, however, one of our chief aims of therapy is to get a prolonged good control of blood glucose to prevent angiopathy in diabetes mellitus (Krall et al. 1971; Takazakura et al. 1975; Job et al. 1976). There have been no proper system to determine insulin regimen. Albisser et al. (1974), Pfeiffer et al. (1975), Clemens (1975), Mirouze et al. (1977), and Kawamori et al. (1978) reported that by using an artificial pancreas, blood glucose could be maintained within an almost physiological range in diabetics.

However, these methods could not be applied upon the diabetics who need insulin treatment throughout their lives for a long time. Therefore, it is necessary to achieve the control of blood glucose as those as possible in its physiological range by the subcutaneous insulin injection.

Lambert et al. (1978) tried to adjust the quantity and the kinds of insulin as close as possible to the physiological pattern of insulin secretion, using their artificial pancreas. However, they could not achieve a very good control of the diurnal variation of blood glucose, in the maximum amplitude of glycemic excursion, or in M-value. This unsatisfactory result may be due to the fact that all of their examines were unstable diabetics. It is likely that another problem lies in their insulin infusion algorithm. The purpose of their algorithm is to maintain the blood glucose within the normal range, so that the insulin-infusion rates vary widely according to changes of blood glucose. The third problem also arises from their algorithm: when the blood glucose becomes too low, glucose is infused according to the algorithm. Therefore, insulin doses so determined for subcutaneous injection may be excessive.

In the present study, blood glucose was regulated well during the examination. This indicates that our insulin infusion algorithm is valuable to control blood glucose in the diabetics requiring insulin injection. Furthermore, insulin regimen calculated from the results of the examination was proper in most cases studied. Insulin doses were slightly reduced in the diabetics in whom control of blood glucose was fair before the test. Seventy percent of the diabetics who were controlled poorly before the test (types B and C) could be controlled well on the insulin regimen calculated from the examination.

However, the good control of blood glucose could not be obtained in three cases of the group C. In all of them, insulin infusion was not required to maintain good levels of blood glucose during the midnight and marked rises of blood glucose were observed in the early morning. In order to control fasting blood glucose in these cases, it was necessary to change evening dose of lente insulin injection to 9:00 p.m. or to change lente insulin in the evening to ultralente insulin, which suggested that elevation of fasting blood glucose in these cases was due to "dawn phenomenon". (Bolli and Gerich 1984).

References

- 1) Albisser, A.M., Leibel, B.S., Ewart, T.G., Davidvac, Z., Botz, C.K., Zingg, W., Schipper, H. & Gander, R. (1974) Clinical control of diabetes by the artificial pancreas. *Diabetes*, **23**, 397-404.
- 2) Bolli, G.B. & Gerich, J.E. (1984) The "dawn phenomenon" — a common occurrence in both non-dependent and insulin-dependent diabetes mellitus. *New Engl. J. Med.*, **310**, 746-750.
- 3) Clemens, A.H. (1975) The artificial endocrine pancreas. A model system for computerized feedback control instrumentation. *Miles Analecta*, **2**, 4-8.
- 4) Cohen, S.L., Legg, S.L. & Bird, R. (1964) A bedside method of blood glucose estimation. *Lancet*, **2**, 883-884.
- 5) Genuth, S. & Martin, P. (1977) Control of hyperglycemia in adult diabetics by pulsed insulin delivery. *Diabetes*, **26**, 571-581.
- 6) Goto, Y. & Kikuchi, H. (1972) Application of the M-value, an index of blood sugar control, for the true blood sugar value. *J. Jap. Diab. Soc.*, **15**, 319-323. (Japanese)
- 7) Jarret, R.J., Keen, H. & Hardwick, C. (1970) "Instant" blood sugar measurement using dextrostix and reflectance meter. *Diabetes*, **19**, 724-727.
- 8) Job, D., Eschwege, E., Guyot-Argenton, C., Aubry, J-P. & Tchobroutsky, G. (1976) Effect of multiple daily insulin injections on the course of diabetic retinopathy. *Diabetes*, **25**, 463-469.
- 9) Kawamori, R., Shichiri, M., Goriya, Y., Yamasaki, Y., Shigeta, Y. & Abe, H. (1978) Importance of insulin secretion based on the rate of change in blood glucose concentration in glucose tolerance, assessed by the artificial beta cell. *Acta endocr.*, **87**, 339-351.
- 10) Kraegen, E.W., Lazarus, L., Meler, H., Campbell, L. & Chia, Y.O. (1975) Carrier solutions for low-level intravenous insulin infusion. *Brit. med. J.*, **3**, 464-466.
- 11) Krall, L.P. (1971) Relationship of quality of treatment and control of diabetes to prognosis. In: *Joslin's Diabetes Mellitus*, 11th ed., edited by A. Marble, P. White, R.F. Bradley & L.P. Krall, Lea and Febiger, Philadelphia, pp. 213-216.
- 12) Lambert, A.E., Buysschaert, M., Marchand, E., Pierard, M., Wojcik, S. & Lambotte, L. (1978) Determination of insulin requirements in brittle diabetic patients by the artificial pancreas. *Diabetes*, **27**, 825-833.
- 13) Mirouze, J., Selam, L., Pham, T.C., Mendoza, E. & Orsetti, A. (1977) Evaluation of exogenous insulin homeostasis by the artificial pancreas in insulin-dependent diabetes. *Diabetologia*, **13**, 273-278.
- 14) Pfeiffer, E.F., Thum, C.H., Beischer, W., Meissner, C., Tamas, G.Y., Jr. & Clemens, A.H. (1975) The artificial pancreas: Application to experimental and clinical research. *Diabetologia*, **2**, 369-370.
- 15) Schlichtkrull, J., Munch, O. & Jersild, M. (1965) The M-value, an index of blood sugar control in diabetics. *Acta med. scand.*, **177**, 95-102.
- 16) Takazakura, E., Nakamoto, Y., Hayakawa, H., Kawai, K., Muramoto, S., Yoshida, K., Shimizu, M., Shinoda, A. & Takeuchi, J. (1975) Onset and progression of diabetic glomerulosclerosis. A prospective study based on serial renal biopsies. *Diabetes*, **24**, 1-9.
- 17) Tchobroutsky, G. (1978) Relation of diabetic control to development of microvascular complications. *Diabetologia*, **15**, 143-152.