Rapid Publication
Closed-Loop Glycemic Control with a Wearable Artificial Endocrine Pancreas
Variations in Daily Insulin Requirements to Glycemic Response

MOTOAKI SHICHIRI, RYUZO KAWAMORI, NOBUYOSHI HAKUI, YOSHIMITSU YAMASAKI, AND HIROSHI ABE

SUMMARY

We succeeded in miniaturizing a needle-type glucose monitoring system with characteristics suitable for application in a wearable, closed-loop control system. A wearable artificial endocrine pancreas (12 × 15 × 6 cm, 400 g) consisting of a sensor, a microcomputer system that calculates insulin and glucagon infusion rates, and two roller pumps was developed.

Continuous glucose monitoring by a glucose sensor inserted in the subcutaneous tissue of the forearm or abdomen of healthy and diabetic volunteers revealed that glucose concentrations in subcutaneous tissue were 10% lower than, but were highly correlated with, blood glucose concentrations in the range of 49–388 mg/dl.

Glycemic control was established in diabetic patients by intravenously infusing insulin in response to measured glucose concentrations on a moment-to-moment basis for a period of several days. By comparing the glycemic control obtained in each patient treated with multiple insulin injections or open-loop subcutaneous insulin infusion, the superiority of feedback control with the system was clearly demonstrated.

During continuous glycemic regulation, day-to-day variations of insulin requirements were recognized in both basal insulin infusion and postprandial insulin infusion rates in response to identical meals and exercise.

These data suggest the feasibility of long-term glycemic control in diabetic subjects with a wearable artificial endocrine pancreas, and indicate that to overcome changes in individual metabolic characteristics on a moment-to-moment basis, a closed-loop glycemic control system may be essential for ambulatory diabetic patients. DIABETES 1984; 33:1200–1202.

This study was presented in part at the 43d and 44th Annual Meetings of the American Diabetes Association.

From the First Department of Medicine, Osaka University Medical School, Osaka, Japan.

Address reprint requests to Dr. M. Shichiri, First Department of Medicine, Osaka University Medical School, 1-150 Fukushima, Fukushima-ku, Osaka, 553, Japan.

Received for publication 15 July 1984.

We succeeded in miniaturizing a glucose-monitoring system into a needle-sized system that preserves sensor characteristics suited to a closed-loop control system. In addition, we developed a wearable artificial endocrine pancreas that effectively controls glycemia in pancreatectomized dogs for a period of 3 days and with replacement of the sensor for up to 7 days.[1,2]

Because the subcutaneous needle sensor provides the critical interface between man and machine, we tested its performance, safety, and feasibility in both healthy and diabetic volunteers. We then attempted glycemic control in diabetic patients with a wearable artificial pancreas system.

MATERIALS AND METHODS

Needle-type glucose sensor. The characteristics and preparation of the needle-type glucose sensor have been previously described.[1,2] In addition, to augment the biocompatibility of the sensor, a hydrophilic polyvinylalcohol membrane was applied to the hydrophobic polyurethane membrane.

Wearable artificial endocrine pancreas. The wearable artificial pancreas system, consisting of a needle-type glucose sensor, microcomputer system, two roller pumps driving the unit for insulin and glucagon infusions, and a lithium battery, was packed into a small unit (12 × 15 × 6 cm) weighing 400 g. The wearable computer system memorizes measured glucose concentrations, insulin infusion rates (IIR), and glucagon infusion rates (GIR) every minute for more than 24 h. A parameter input–data output device was connected to the wearable artificial endocrine pancreas when parameters in the insulin and glucagon infusion algorithms were changed, or to record the output from the glucose sensor and the hormone pumps for clinical records. Algorithms for intravenous infusion of insulin and glucagon in the system are the same as those of our bedside system.[3–6] IIR(t) (mU/kg/min) is expressed as follows: $IIR(t) = Kp\ BG(t) + Kd\ dBG(t)/dt + Kc$, where BG(t) and dBG(t)/dt are glucose

concentration (mg/dl) and its rate of change (mg/dl/min) at time t, respectively, Kp and Kd are coefficients for proportional and derivative action, respectively, and Kc is a constant for basal insulin supplementation. By selecting proper parameters (Kp = 0.0281, Kd = 0.269, and Kc = −2.02), this algorithm was proven to establish perfect glycemic control with physiologic plasma insulin profiles,[5,6] and these parameters were used in glycemic control in the present study. GIR(t) (ng/kg/min) is expressed as follows: GIR(t) = Gp (BGp − BG[t − τ]) + Gd (−dBG [t −τ]/dt), where Gp and Gd are coefficients for proportional and derivative action, respectively. BGp is projected blood glucose concentration for recovery from hypoglycemic state. τ is time lag (min) for glucagon infusion. By selecting parameters (Gp = 0.2, Gd = 0.4, BGp = 60, τ = 10), this algorithm will begin to operate only when blood glucose concentration falls below 60 mg/dl.

Glucose monitoring by means of a glucose sensor inserted into subcutaneous tissues of human subjects. Needle glucose sensors were inserted into subcutaneous tissue of forearm or abdomen of seven healthy and three diabetic volunteers. The results obtained using these glucose sensors were compared with the results of simultaneous intravenous glucose monitoring using a bedside artificial endocrine pancreas. Glucose data were compared during either oral glucose challenges or standard meals.

Blood glucose regulation in diabetic subjects with a wearable artificial endocrine pancreas. In five hospitalized insulin-dependent diabetic patients glycemic control was attempted with the wearable artificial endocrine pancreas. The sensor was inserted in the subcutaneous tissue of the forearm, and insulin and glucagon were infused intravenously. The whole system was kept in the pocket of a jacket. Concentrations of insulin and glucagon solutions used were 2 U/ml and 20 ng/ml, respectively. Reservoirs containing 20 ml of each hormone solution were replaced twice daily. The outputs of the glucose sensors were compared with the results of intravenous glucose monitoring using the bedside artificial endocrine pancreas or by discretely measuring blood glucose. In each patient, glycemic control obtained with intermediate-acting insulin injected once a day, multiple insulin injections, and open-loop subcutaneous insulin infusion regimens was compared by means of the M-value,[7] mean blood glucose concentration (MBG), and mean amplitude of glycemic excursions (MAGE)[8] calculated from blood glucose concentrations obtained before and 1 and 2 h after meals, at 11:00 p.m., and before breakfast the next day. Continuous glycemic control with the wearable artificial endocrine pancreas was extended for up to 6 days by replacing the sensors every fourth day. The caloric content and composition of meals were held identical in each patient. The patients were allowed to walk for 30 min starting at 1 h after each meal.

Results were expressed as mean ± SD. Student's *t*-test was used for statistical analysis.

RESULTS

Glucose concentrations in subcutaneous tissue (Y) were highly correlated with blood glucose concentration (X), (Y = 0.79X + 17, N = 115, r = 0.96) in the range of 49–388 mg/dl. The mean time of the rise in sensor output to reach a steady state of blood glucose concentration was 5.1 min. There was no difference in the values obtained in subcutaneous tissue of either forearm or the abdomen.

The 6-day continuous blood glucose regulation achieved by the wearable system in an insulin-dependent diabetic patient is shown in Figure 1. The pattern of glycemia was indistinguishable from a normal physiologic blood glucose pattern over the 6-day study. Since glucose concentrations never fell below 60 mg/dl, the glucagon infusion mechanism did not operate at all. Control of blood glucose was achieved entirely through variable insulin infusion. It was also found with the wearable artificial endocrine pancreas system that day-to-day variations in the glycemic response occurred despite identical meal intake patterns and exercise in the same patient (MBG, 116–131 mg/dl; M-value, 4.7–9.4; MAGE, 43–80 mg/dl). These fluctuations in blood glucose levels resulted in a remarkable variation in the rates and pattern of insulin infusion. Variations in insulin requirements were up to 12 U/day and in the range of 3–10 U for achieving postprandial glycemic control. Comparison of the glucose regulation in the five patients during the four treatment regimens is summarized in Table 1. All the indices of glycemic

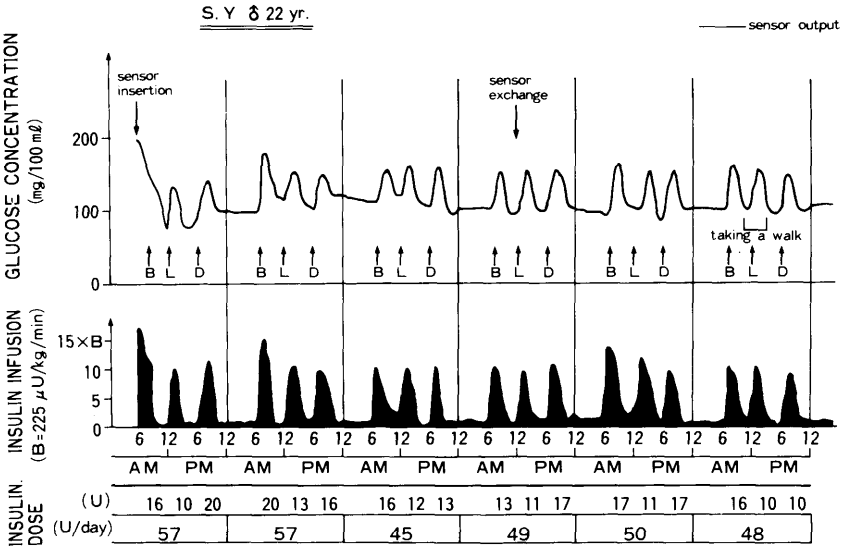

FIGURE 1. A 6-day continuous glycemic control in insulin-dependent diabetic patient with a wearable artificial endocrine pancreas. The sensor was replaced on the fourth day. The patterns of insulin infusion and cumulative insulin requirement doses are also depicted.

TABLE 1
Blood glucose regulatory indices in various kinds of insulin treatment regimens in five insulin-dependent diabetic subjects

Treatment	N	M-value	MBG (mg/dl)	MAGE (mg/dl)
Intermediate	5	42.2 ± 10.2*	158 ± 50	150 ± 50*
Multiple	5	18.0 ± 4.6*	151 ± 7*	105 ± 23*
CSII†	5	13.6 ± 2.6*	126 ± 12*	94 ± 15*
WAEP	5	8.4 ± 2.8	106 ± 11	56 ± 13

Data are expressed as mean ± SD.
*$P < 0.05$ versus glycemic control with WAEP.
†CSII, continuous subcutaneous insulin infusion.

regulation (MBG, 106 ± 11 mg/dl; M-value, 8.4 ± 2.8; MAGE, 56 ± 13 mg/dl) during application of the wearable closed-loop control system were significantly smaller than those values obtained by intermediate-acting insulin once a day, multiple insulin injection, or open-loop continuous subcutaneous insulin infusion regimens, respectively ($P < 0.05$).

DISCUSSION

With regard to the safety of glucose oxidase used in the glucose sensor, we demonstrated that when glucose oxidase was immobilized with glutaraldehyde to cellulose diacetate, there was no detectable leakage of glucose oxidase from the sensor as judged by measuring glucose oxidase concentration in the perfusate of an in vitro circulation. Furthermore, no significant increase in total immunoglobulin concentration bound to glucose oxidase as measured with a double-antibody method was found in sera obtained from human volunteers after repeated application of the glucose sensor in their subcutaneous tissue.[9] These data indicate that the glucose sensor in which glucose oxidase is bound to cellulose diacetate is safe and suitable for clinical application. In the present study we demonstrated that even though sensor outputs might depend on local conditions such as extracellular fluid circulation and oxygen availability, our sensors were rather stable in human subcutaneous tissue.

By intravenously infusing insulin in response to measured glucose concentrations with the aid of a wearable artificial endocrine pancreas system, it was possible to closely regulate glycemia even in ambulatory diabetic subjects. This was true despite spontaneous day-to-day variation in glycemia and insulin requirements in the diabetic subjects controlled with a wearable artificial endocrine pancreas. Three potential factors could contribute to changes in sensor-measured glycemia: changing function of the sensor per se, changing rates of perfusion of extracellular fluid through surrounding tissues in the region of the sensor, and changing metabolic state of individual patients during the course of the study.

The output characteristics of the needle-type glucose sensor were examined during 3 days of continuous tissue glucose monitoring and were found to be relatively constant. On the fourth day, sensor output current relative to blood glucose concentration determined from discretely obtained blood samples decreased to 74% of the initial value and the relative response time of the sensor was prolonged to 13.5 min from 5.1 min, compared with the freshly implanted sensor. In vitro characteristics of the sensor determined after removal of the sensor showed a 23% reduction in output current and prolongation of response time to 43 s from 29 s. The biocompatibility of the membrane of sensors kept in subcutaneous tissue for 3 days was examined by electron microscopy. Fixation of protein on the membrane was recognized; thus, the decrease in output current of sensors after 3 days of continuous subcutaneous use may be caused by the depression of the sensor secondary to protein deposition on the membrane. Histologic changes in subcutaneous tissue around the sensor-insertion area were examined in normal dogs. After a 3-day application, migration of leukocytes and slight fibrin deposition was recognizable in the insertion area. These changes could result in decreased perfusion of fluid through surrounding tissues and could therefore be one cause of time delay in sensor response. The sensor-related problems will be approached through alterations in membrane design such as varying the combination of hydrophilic and hydrophobic components of the sensor membrane. As an explanation for the observed glycemic variability, however, moment-to-moment variation in individual patients' metabolic characteristics seem to be the more important factor, since daily replacement of the sensor did not prevent daily variations of glycemic excursions. Metabolic characteristics that could be changing include variations in meal ingestion and absorption and in insulin sensitivity. Thus, we suggest that a closed-loop glycemic control system suitable for the ambulatory diabetic patient may be necessary to overcome the spontaneous metabolic changes that seem to characterize the insulin-dependent diabetic subject.

ACKNOWLEDGMENTS

We are indebted to Dr. M. Kosuga (Director, Medical Supplies and System Group, Fujisawa Pharmaceutical Co., Osaka, Japan) and his staff for their cooperation.

This study was supported in part by a grant from the Research Development Corporation of Japan.

REFERENCES

[1] Shichiri, M., Kawamori, R., Yamasaki, Y., Hakui, N., and Abe, H.: Wearable-type artificial endocrine pancreas with needle-type glucose sensor. Lancet 1982; 2:1129–31.

[2] Shichiri, M., Kawamori, R., Goriya, Y., Yamasaki, Y., Nomura, M., Hakui, N., and Abe, H.: Glycaemic control in pancreatectomized dogs with a wearable artificial endocrine pancreas. Diabetologia 1983; 24:179–84.

[3] Kawamori, R., Shichiri, M., Goriya, Y., Yamasaki, Y., Shigeta, Y., and Abe, H.: Importance of insulin secretion based on the rate of change in blood glucose concentration in glucose tolerance, assessed by the artificial beta cell. Acta Endocrinol. Copenh. 1978; 87:339–51.

[4] Goriya, Y., Kawamori, R., Shichiri, M., and Abe, H.: The development of an artificial beta cell system and its validation in depancreatized dogs: the physiological restoration of blood glucose homeostasis. Med. Prog. Technol. 1979; 6:99–108.

[5] Shichiri, M., Kawamori, R., and Abe, H.: Normalization of paradoxic secretion of glucagon in diabetics who were controlled by the artificial beta cell. Diabetes 1979; 28:272–75.

[6] Kawamori, R., Shichiri, M., Kikuchi, M., Yamasaki, Y., and Abe, H.: Perfect normalization of excessive glucagon responses to intravenous arginine in human diabetes mellitus with the artificial beta cell. Diabetes 1980; 29:762–65.

[7] Schlichtkrull, J., Munk, O., and Jersild, M.: The M-value, an index of blood-sugar control in diabetes. Acta Med. Scand. 1965; 177:96–102.

[8] Service, F. J., Molnar, G. D., Rosevear, J. W., Ackerman, E., Gatewood, L. C., and Taylor, W. F.: Mean amplitude of glycemic excursions, a measure of diabetic instability. Diabetes 1970; 19:644–55.

[9] Shichiri, M., and Kawamori, R.: Feasibility of needle-type glucose sensor and the wearable artificial endocrine pancreas system in human diabetes mellitus. *In* Diabetes Treatment with Implantable Insulin Infusion Systems. Irsigler, K., Kritz, H., and Lovett, R., Eds. Munich, Urban and Schwarzenberg, 1983:224–30.