Medical Grand Rounds: Open and Closed Loop Insulin Delivery Systems in Diabetes: Current Status

F. John Service
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To introduce this discussion of the current status of open and closed loop systems for insulin delivery in the treatment of diabetes mellitus, I will first discuss the historical perspectives which indicate the need for such devices. Reference to events in nondiabetics provides a good starting point (1).

No major spontaneous perturbations of plasma glucose concentration occur in the absence of food intake or exercise when healthy individuals are fasted for three days (Fig. 1). The glucose concentration gradually declines, and the serum insulin level falls while plasma glucagon increases. By contrast, in the fed state, plasma glucose concentration increases in response to a meal and returns to basal levels in the interprandial period. As expected, the increase is smaller with a smaller amount of food. Overnight, the plasma glucose concentration remains stable between 75 and 100 mg/dl (Fig. 2). Par passu with the changes in plasma glucose concentration are changes in the secretion of the insulinotropic gut hormone, gastric inhibitory polypeptide, and consequently, plasma insulin levels. In the fed state, however, plasma glucagon levels do not change importantly (Fig. 2).

Conventional treatment of insulin-requiring diabetic patients fails to achieve normoglycemia (Fig. 3). Changes in plasma glucose concentration are expressed as mean amplitude of glycemic excursions (MAGE), which has a mean value of 44 for nondiabetics but an even higher value for stable diabetics (67). Mean blood glucose concentration is 83 mg/dl for normal subjects and 111 mg/dl for this group of patients with stable diabetes. The unstable diabetic patients (insulin dependent diabetes mellitus, IDDM) experience wider excursions and a higher mean blood glucose concentration. The mean of daily differences in blood glucose (MODD) is very narrow for nondiabetic subjects, somewhat larger for patients with stable diabetes, and very large for those with unstable diabetes.

Why has it been impossible with current modes of insulin therapy to normalize blood glucose concentrations in insulin-requiring diabetic patients? A number of theories over the years have attempted to explain the lability of diabetes in some patients: the effect of depot insulins, the Somogyi phenomenon, and errors by the physician or patient. Important to our understanding is the demonstration that insulin dependent or unstable diabetic patients are totally deficient in insulin, whereas non-insulin dependent or stable diabetic patients retain some insulin secretory reserve (Fig. 4). The failure to

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achieve normal glycemia or normoglycemia in insulin deficient diabetics is an indictment of current modes of insulin administration. We are not able to achieve normal plasma glucose concentrations because we do not deliver the right kind of insulin in the right amounts at the right time in the right place.

Research efforts in the early 1970s led to the development of two major systems for insulin delivery: closed loop and open loop systems. In the closed loop system, blood glucose concentrations are monitored continuously by a glucose sensor, and the results are directed to a computer which, in response to a number of algorithms, determines the rates of infusion of insulin. Open loop systems were developed concurrently with closed loop systems. The open loop system is missing one vital component — the glucose sensor, because the technology required for a chronic “in-dwelling” reliable glucose sensor is not yet available. Some clinical and research applications of closed loop systems are shown in Table I.

Many technical factors were involved in the development of open loop systems. The insulin pump may be one of several types: syringe, peristaltic, bellows, or piston displacement. At present, insulin cannot be administered directly into the portal vein, the physiologic route. Alternate routes which have been used include peripheral, intravenous, subcutaneous, and intraperitoneal administration. With respect to the infusion of insulin for prandial glucose control, factors such as the timing and rate and shape of the infusion vary from system to system and are influenced by the chosen route of insulin administration. By far the largest experience using open loop devices has been with the subcutaneous route with considerably less for the intraperitoneal and peripheral venous routes. The optimal route for insulin administration has not been determined.

By using the Biostator to determine the insulin infusion rates after the ingestion of a mixed meal in alloxan diabetic dogs, we observed no differences in plasma glucose concentrations or flux rates or plasma insulin between the subcutaneous and the intraperitoneal routes or between the portal and peripheral venous routes of insulin administration (2). The Biostator is useful in patterning the insulin infusion rates for an open loop device.

TABLE I
Clinical and Research Uses of an Artificial Endocrine Pancreas

Clinical
Control of glycemia of diabetes
a) During labor and delivery
b) During surgery
c) For ketoacidosis or hyperosmolar nonketotic coma
Control of glycemia in insulinoma during pancreatic exploration
Generation of insulin doses for diabetes
a) In portable insulin infusion devices
b) For conventional or intensive insulin therapy

Research
Effect of short-term normoglycemia in diabetes on
a) Glycosylated hemoglobin
b) Peripheral nerve function
c) Substrate concentrations and flux rates
d) Glucoregulatory hormones
Achievement of euglycemia for several hours in diabetes before studies of acute insulin deficiency
Glucose clamp studies
Assessment of insulin requirements
a) Overnight
b) For meals of same or different size at different times of the day
Comparison of different routes for insulin administration

Fig. 2
Circulating glucose, insulin, gastric inhibitory polypeptide (GIP), and glucagon levels are shown for six healthy subjects under ambulatory conditions for 24 hours. Fork-spoon-knife drawing represents a mixed meal; the single spoon is a snack. Glucose, GIP, and insulin are perturbed from the basal state only with food ingestion. With overnight fasting, the basal levels are restored. From Service and Nelson (1); reproduced with permission of the American Diabetes Association, Inc.
Insulin Pumps

Three quantitative measurements: MBG, mean blood glucose; MAGE, mean amplitude of glycemic excursions; MODD, mean of daily differences of blood glucose — of normal, stable diabetic, and unstable diabetic subjects studied with continuous blood glucose analysis while subjects pursued normal activities (Modified from Molnar GD, Taylor WF, Langworthy A: On measuring the adequacy of diabetes regulation: Comparison of continuously monitored blood glucose patterns with values at selected time points. Diabetologia 1974;10:139-43. By permission of Springer-Verlag, Berlin). From Service and Nelson (1); reproduced with permission of the American Diabetes Association, Inc.

(Figs. 5,6). When the amounts of insulin given for each meal were administered as a bolus 30 minutes before the meal and the basal infusion given by the open loop device was a single injection of ultralente insulin before breakfast (Fig. 7), plasma glucose control was comparable to that achieved by open loop and Biostator studies. The observation of similar glucose control between continuous subcutaneous insulin infusion using an open loop device and intensive conventional insulin therapy has been demonstrated by others in outpatients. This observation cautions against the indiscriminate use of open loop devices. In addition, insulin pumps have technical problems: needles dislodge in the subcutaneous route, catheters break, pumps break, batteries fail. Patients receiving chronic subcutaneous insulin infusion therefore may develop diabetic ketoacidosis when the infusion of insulin is interrupted. In addition, episodes of severe hypoglycemia during the use of open loop systems have been reported. It is legitimate, therefore, to question whether or not open loop devices are necessary. Accumulating experience indicates that neither open loop devices nor intensive conventional insulin therapy will achieve total normalization of glycemia. Of course, we do not know how close to normal glycemia must be achieved to prevent the degenerative complications of diabetes, even if there is indeed an effect of hyperglycemia on degenerative sequelae of diabetes mellitus.

Dr. Fred Whitehouse*
With intraperitoneal infusion, does insulin enter the portal vein system, the inferior vena cava, or both?

Dr. Service
Available data in this regard are not unequivocal. Studies

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CLOSED-LOOP INTRAVENOUS INFUSION


OPEN-LOOP SUBCUTANEOUS INFUSION

Plasma glucose and free insulin concentrations in a group of insulin dependent diabetic subjects during treatment with an open loop subcutaneous insulin infusion system. The diabetics are the same subjects as described in Figure 3. B = breakfast, L = lunch, D = dinner, S = snack. From Service and Nelson (1); reproduced with permission of the American Diabetes Association, Inc.

MULTIPLE SUBCUTANEOUS INJECTIONS

Plasma glucose and free insulin concentrations in a group of insulin dependent diabetic subjects during treatment with intensified conventional therapy. Regular insulin was injected 30 minutes before each meal and ultralente insulin before breakfast. The diabetic subjects are the same as those described in Figure 3. B = breakfast, L = lunch, D = dinner, S = snack. From Service and Nelson (1); reproduced with permission of the American Diabetes Association, Inc.

Dr. Whitehouse

Is it possible that an implantable insulin pump infusing a basal insulin dose can convert a Type I diabetic patient into a Type II diabetic patient? For example, infusing one-half or three-fourths unit of insulin per hour? In this way can we convert an insulin dependent diabetic into a non-insulin dependent diabetic mechanically?

Dr. Service

Your idea presents a very interesting possibility. There is experience with implanting a pump into patients with non-insulin dependent diabetes hoping that provision of basal insulin requirements will enable those subjects to meet the insulin demands of a meal from their own reserves. I am not aware of such an approach for insulin using radioactive insulin administered to anesthetized dogs indicate that the insulin is absorbed preferentially into the portal vein based on the appearance of radioactivity in the portal vein and the femoral artery. That control of the blood glucose is improved when insulin is administered into the portal rather than caval system has not been rigorously proved.
Insulin Pumps

dependent diabetics. There is an implantable, single-rate infusion pump which has a multiple orifice dial, and the orifice size can be changed electromagnetically to provide increased rates of infusion with meals. But this instrument has not yet been perfected.

In our patients who receive a morning dose of ultralente insulin plus multiple injections of regular insulin correlated with food intake, our results after six months have been acceptable. We have had no instances of ketoacidosis which would constitute a threatening complication if the insulin pump fails in any way.

References