Why Intraperitoneal Delivery of Insulin
With Implantable Pumps in NIDDM?
WILLIAM C. DUCKWORTH, CHRISTOPHER D. SAUDEK, AND ROBERT R. HENRY

In the normal state, pancreatic secretion of insulin results in a portal/peripheral gradient with the highest concentrations of insulin in the liver. In diabetic patients with absent or insufficient pancreatic insulin secretion who require exogenous insulin, this normal gradient is lost, resulting in numerous abnormalities. This consideration led to interest in the intraperitoneal delivery of insulin, hoping to produce a therapeutic state more closely resembling normal physiology. The development of implantable insulin pumps, which can deliver insulin intraperitoneally, led to numerous studies on insulin-dependent diabetes mellitus (IDDM) patients, demonstrating that insulin delivered intraperitoneally is rapidly and predictably absorbed with most of it going into the portal system, resulting in hepatic delivery of insulin. Studies in IDDM patients have demonstrated that good glucose control can be achieved with intraperitoneal delivery of insulin from implantable pumps with lesser glycemic fluctuations and, therefore, fewer episodes of hypoglycemia. Furthermore, intraperitoneal insulin results in carbohydrate and particularly lipid metabolism that more closely mimics the normal physiological state than produced by injections of insulin. Thus, implantable insulin pumps are being studied for use in IDDM. Many non-insulin-dependent diabetes mellitus (NIDDM) patients have insufficient pancreatic secretion and require exogenous insulin. Because of alterations in hepatic sensitivity to insulin, increments in insulin delivery to the liver may be even more important in NIDDM than IDDM. Furthermore, insulin resistance, which is an integral part of NIDDM, results in higher physiological levels of insulin, which are required for glucose control, and thus significant peripheral hyperinsulinemia occurs in patients receiving exogenous insulin. Because of hepatic extraction, intraperitoneal administration of insulin in NIDDM could provide sufficient insulin to the liver to control hepatic metabolism and reduce peripheral insulin levels, the risk for atherosclerosis, and other adverse effects of hyperinsulinemia. Because of these considerations, a Veterans Affairs Cooperative Study examining the use of implantable insulin pumps delivering intraperitoneal insulin in NIDDM patients was initiated to determine whether this is a feasible approach to NIDDM patients' therapy and whether this results in beneficial effects on carbohydrate and lipid metabolism and peripheral insulin levels. Diabetes 41:657-61, 1992

V

From the Department of Veterans Affairs Medical Center, and the Department of Internal Medicine, University of Nebraska Medical Center, Omaha, Nebraska, the Department of Medicine, Division of Endocrinology and Metabolism, Johns Hopkins University School of Medicine, Baltimore, Maryland; and the Department of Veterans Affairs Medical Center, San Diego, California.

Address correspondence and reprint requests to Dr. William C. Duckworth, University of Nebraska Medical Center, 600 South 42nd Street, Omaha, NE 68198-3029.

Received for publication 3 December 1991 and accepted in revised form 2 January 1992.
Study on the relationship between glycemic control and diabetic complications in NIDDM.

Because glycemic control can, at least theoretically, be established with less invasive, less expensive approaches, the question must be asked: Why implantable insulin pumps? Patients may focus on freedom from injections and quality of life issues, but from a scientific viewpoint, the most significant feature of implantable pumps is that insulin is delivered into the peritoneal space.

This article summarizes the information available on intraperitoneal insulin delivery. We consider the evidence that it may be more rapidly and consistently absorbed, that it is preferentially absorbed into the hepatic portal venous system, and that this hepatic delivery may beneficially affect lipid metabolism and peripheral hyperinsulinism.

Peritoneal delivery of insulin results in more rapid and more consistent absorption than peripheral injection, resulting in a more reliable and predictable delivery of insulin into the circulation (2). This delivery provides predictable increases in circulating insulin that are particularly important for controlling postprandial glycemia and also allows a return to low basal levels between meals. Subcutaneously injected intermediate and long-acting insulins frequently produce persistent hyperinsulinism that is quite different from the normal pancreas' return to a very low basal secretory rate between meals. In a study comparing free insulin profiles after intraperitoneal, intramuscular, and subcutaneous insulin administrations, intraperitoneal insulin delivery produced serum insulin peaks at 15 min, whereas intramuscular and subcutaneous insulin injections resulted in a slower rise of plasma free insulin, peaking at 60 and 90 min, respectively (3). Insulin delivered to the upper peritoneum was more quickly absorbed than that delivered to the lower peritoneum. Although obviously the insulin peak can be adjusted to match food absorption by giving subcutaneous insulin further in advance of the meal, the difficulty of estimating when exactly to eat increases as insulin absorption is slowed. In addition, the rapidity of increase in plasma insulin is important in limiting postmeal glucose rises. In NIDDM, this is demonstrated by the deleterious effect of loss of acute (first-phase) insulin response to glucose, resulting in postprandial hyperglycemia, even with a normal total insulin response.

Recognizing the importance of the rate of increase in plasma insulin in controlling postprandial glycemic excursions resulted in development of insulin analogues that are more rapidly absorbed and produce rapid increases in plasma insulin levels (4). Several of these analogues were developed and are being tested for use in the clinical management of diabetes. These insulin analogues have altered amino acid sequences, which prevent dimerization and/or aggregation, resulting in faster absorption from subcutaneous tissues and thus rapid increases in plasma insulin levels. Although these analogues may ultimately become clinically useful, a full understanding of their biological properties must be established before extensive use (5,6). Direct comparisons have not been conducted, but intraperitoneal insulin may provide the same advantage in terms of rapidity of absorption.

In addition to speed of absorption, variability of absorption and local degradation of subcutaneous insulin may contribute to glycemic liability in diabetes, leading to great difficulty in managing certain patients (7). Extensive degradation of insulin in the subcutaneous space is a rare cause of severely "brittle" diabetes (8), but variation in insulin absorption due to factors such as depth and location of injection, exercise of an extremity, or vascularity of the tissue is a common cause of unpredictably wide swings in blood glucose levels. This liability may contribute not only to long-term complications but may lead to immediate morbidity and hospitalization, resulting in increased health-care costs or even mortality (9). Implanted insulin pumps delivering intraperitoneal insulin alleviate these variables in absorption and degradation and thus may assist in managing unstable diabetes (10,11). Although subcutaneous insulin degradation has been recognized primarily in IDDM, issues of variable insulin absorption undoubtedly affect glycemic control in insulin-requiring NIDDM patients also.

Theoretically, the greatest advantage of intraperitoneal insulin delivery is that the insulin is absorbed preferentially into the portal system and delivered initially to the liver in a more physiological manner compared with subcutaneous injections (12). It seems logical that physiological delivery of insulin to the liver should produce more normal metabolism of glucose and other metabolites than peripherally delivered insulin. However, relatively few studies in humans have carefully examined this issue. Studies in dogs have shown conflicting results: 1) the portal route of insulin delivery may be necessary if fasting metabolite and hormone levels are to approximate normal (13,14) or 2) portal and peripheral insulin delivery comparably regulate hepatic and extrahepatic carbohydrate metabolism (15). In contrast to the situation in dogs, however, the pathophysiology of NIDDM may be uniquely suited to delivery of insulin to the liver via the portal vein. Excessive basal hepatic glucose output is the principal abnormality contributing to elevated fasting plasma glucose levels in NIDDM (16), and a close correlation has been shown repeatedly to exist between these parameters (17). Furthermore, in both nondiabetic and NIDDM subjects, hepatic glucose output is much more sensitive to suppression by insulin than is stimulation of peripheral glucose uptake (18). Thus, increments in circulating insulin levels have a greater impact on the liver than the periphery. This information, coupled with the knowledge that a large first-pass extraction of portal insulin occurs across the liver, emphasizes that intraperitoneal insulin delivery can selectively inhibit increased hepatic glucose output and thereby reduce fasting plasma glucose levels in NIDDM with less peripheral hyperinsulinemia than with subcutaneous insulin injections.

In studies in humans, blood glucose levels can clearly be made normal with either intraperitoneal or subcutaneous insulin. As shown with the studies comparing rapidly absorbed insulin analogues with standard insulin therapy, postmeal glycemic excursions are not returned to
normal with standard subcutaneous insulin therapy. Although careful studies examining this phenomenon and comparing intraperitoneal and subcutaneous insulin in controlling postprandial glucose excursions remain to be conducted, the known characteristics of intraperitoneal insulin absorption suggest that it should be at least as effective as insulin analogues in controlling glyce mia (219–21).

As mentioned above, average blood glucose levels and glycosylated hemoglobin values can be returned to normal with either intensive subcutaneous insulin therapy or intraperitoneal insulin therapy. A consistent advantage of intraperitoneal insulin pump therapy has been that the improved mean plasma glucose is achieved with fewer glycemic excursions so that the difference between low and high glucose values during a day on intraperitoneal insulin is less than when subcutaneous insulin is used, as shown in Saudek et al.’s (22) study of 18 patients before and after pump implantation. Glycemic fluctuations were significantly less with pump therapy than with intensive subcutaneous insulin therapy, and the frequency of hypoglycemia (blood glucose levels <2.8 mM [50 mg/dl]) was reduced from 3.5 to 1.1% with pumps. This reduction in mean glyce mia without an increase in incidence of hypoglycemia, if confirmed, would be a particularly important advantage, given the Diabetes Control and Complications Trial experience of a two- to threefold increased frequency of severe hypoglycemia when tight control is established by intensive subcutaneous insulin therapy (23).

Relatively few data are available on other carbohydrate metabolites, although one study suggested that intraperitoneal insulin was necessary to normalize lactate levels compared with subcutaneous insulin (24). However, another trade-off for normalizing glucose levels with subcutaneous insulin is that higher levels of peripheral insulin are required than with intraperitoneal insulin, which may have deleterious effects, as discussed further below.

More information is available about how peripheral and intraperitoneal insulin delivery affects lipid metabolism in humans. One study found a reduction in the cholesterol content of high-density lipoprotein in patients treated with intraperitoneal insulin compared with subcutaneous insulin with no change in apolipoproteins A-I and A-II, the major proteins of high-density lipoprotein. These investigators postulated that this decrease might reflect an increase in reverse cholesterol transport and thus prove advantageous (24). In more recent studies presented at the IDF meeting in 1991, this same group directly measured reverse cholesterol transport and found an increase in cholesterol efflux after pump implantation and an increase in cholesterol ester transport protein activity, strongly supporting an increase in reverse cholesterol transport (25). In another study, lipids were compared in patients receiving either continuous subcutaneous insulin infusions or intraperitoneal insulin delivered via implantable pumps. Each regimen was used for at least 1 mo and patients were treated in random order. As in essentially all of the studies comparing subcutaneous and intraperitoneal insulin, peripheral insulin levels were lower with peritoneal insulin. Intraperitoneal insulin was associated with lower very-low-density lipoprotein triglycerides and lower very-low-density lipoprotein apo lipoprotein B and higher high-density lipoprotein and high density lipoprotein, cholesterol. The conclusion was that the more physiological intraperitoneal insulin therapy is associated with lipoprotein profiles of lower atherogenic potential (26). Bagdade et al. (27) examined cholesterol ester transfer in patients with IDDM while on intensive subcutaneous insulin therapy and then after an implanted intraperitoneal infusion pump. In these studies, intensive subcutaneous insulin therapy resulted in an increase in cholesterol ester transfer, which was returned to near-normal levels with intraperitoneal insulin in all cases without any change in plasma lipids. After 6 mo of intraperitoneal treatment, the levels of cholesterol ester transfer further improved and approximated closely that of control subjects. The conclusions of this group were that intraperitoneal insulin was more physiological and corrected a key step in reverse cholesterol transport in patients with IDDM (27).

These studies support the overall concept that initial delivery of insulin to the liver alters lipids and lipid turnover in a manner that may reduce atherogenic potential over time. Other hepatic functions that are dependent on insulin also may be improved with intraperitoneal administration, resulting in more physiological portal-peripheral ratios of hormone. For example, intraperitoneal insulin results in higher levels of plasma (25), hydroxy vitamin D levels than subcutaneous insulin, even with comparable glucose control (28).

Because the liver is the primary site for insulin clearance, portal insulin delivery results in first-pass clearance of a significant fraction of insulin. Although clearance rates vary under different conditions, on average the liver removes ~50% of the insulin delivered to it (29). For any given dose of insulin, the amount that reaches the peripheral circulation is considerably less when the insulin is delivered intraperitoneally rather than subcutaneously. It remains to be seen from larger studies whether the total dose of exogenous insulin required for glucose control is, in general, equivalent whether the insulin is delivered intraperitoneally or subcutaneously (22), or reduced with intraperitoneal delivery as might be expected in NIDDM, given the importance of the liver in this disease. But there is no doubt that with intraperitoneal delivery, the peripheral levels of circulating insulin are less than with subcutaneous administration (26). The importance of this issue is emphasized by the mounting evidence that circulating insulin levels may be directly related to the risk for atherosclerosis (30–32). Thus, reduction of circulating insulin levels is a primary theoretical advantage of intraperitoneal insulin, and further study of the effects of lessening peripheral hyperinsulinism is of interest, especially in the treatment of labile insulin-requiring NIDDM. Advantages of maintaining normal or near-normal glucose levels in avoiding diabetic complications may be obscured if the maintenance of these normal glucose levels is achieved at the cost of high circulating insulin levels. Analogously the difficulty may be of showing a benefit in treating hypertension on the incidence of myocardial infarctions, perhaps due to
deleterious effects of the antihypertensive agents being used on lipid or perhaps even insulin levels.

The above-discussed potential advantages of intraperitoneal insulin delivery would, of course, be realized only if implantable insulin pumps are safe and effective. Although it is not the purpose of this discussion to review in-depth the status of pump trials, current information suggests that implantable insulin pumps may be a safe and effective approach to treating, at least, IDDM (22,33,34).

Long-term multicenter studies are under way with two pumps, one manufactured by MiniMed Technologies (Sylmar, CA) and another by Insuflaid (Weston, MA). The initial experience with both pumps was presented at the 14th International Diabetes Federation Congress in June 1991. Each manufacturer has >100 patients enrolled in the studies, and each trial is being conducted in >15 centers in the U.S. and Europe. The major recurrent adverse event has been intraperitoneal catheter blockage with peritoneal tissue or fibrin-containing material, but this complication has been correctable in most cases by laparoscopy. In the Insuflaid pump, there is a second septum located at the proximal end of the catheter that allows flushing the catheter or lavaging the pump unit. This port has been used to correct some pump slow downs but has also resulted in some technical complications. In the Insuflaid trial, some catheters were placed in the superior vena cava, others in the peritoneum. The intravenous route was less satisfactory, with dislodgment of five intravenous catheters, and catheter obstruction occurring in 50% of the intravenous catheters but only 16% of the intraperitoneal catheters (35).

In the MiniMed trial, all catheters were in the peritoneum, and obstruction occurring at a rate that, at least initially, is <0.2/patient-yr. All implanted pumps have functioned safely with no occurrence of overdelivery or total stoppage. Work is being continued on improving catheter design and composition and the rate of occlusion appears low enough to warrant continued studies. As mentioned above, these trials also have suggested that there are reduced glycemic excursions resulting in normal or near-normal average blood glucose levels with fewer hyper- and hypoglycemic swings. Selam et al. (35) reported that the rate of significant hypoglycemic events fell from 0.47 to 0.02/patient-yr when intraperitoneal insulin infusion replaced intensive control with subcutaneous insulin therapy.

Most of the clinical experience with implantable insulin pumps in NIDDM is limited to an earlier Insuflaid pump that provided only basal rate intravenous insulin (36,37). Conclusions were that tolerance of the devices was excellent, as has been the experience with IDDM, and plasma glucose could be controlled in or near the normal range for 3 yr. One problem in this study was alteration of the insulin in the pump after residing there for some time, but newer preparations of insulin have greatly reduced this problem (38).

The past and ongoing clinical trials, then, suggest at least that implantable insulin pumps are safe and effective enough to justify further clinical research. Insulin delivered into the hepatic portal system is rapidly and consistently absorbed, has beneficial effects on lipid and lipoprotein metabolism, and appears to prevent peripheral hyperinsulinism. Accordingly, a major focus of that research ought to be the careful evaluation of how intraperitoneal insulin might affect the serious metabolic aberrations found in NIDDM.

ACKNOWLEDGMENTS
This article was supported by funds from the Veterans Affairs Medical Research Program and by U.S. Public Health Service Grant RR-00035.

APPENDIX: PARTICIPANTS IN VA COOPERATIVE TRIAL 344A
Cochairmen: William C. Duckworth, MD and Christopher S. Saudek, MD
Principal Investigators: Sue Kirkman, MD, Frederick L. Dunn, MD, VA Medical Center, Durham, NC; James W. Anderson, MD, VA Medical Center, Lexington, KY; Robert Anderson, MD, VA Medical Center, Omaha, NE; David E. Kelley, MD, VA Medical Center, Pittsburgh, PA; Frank Zieve, MD, PhD, Robert A. Adler, MD, VA Medical Center, Richmond, VA; Kenneth Feingold, MD, VA Medical Center, San Francisco, CA; and Robert R. Henry, MD, Steven V. Edelman, MD, VA Medical Center, San Diego, CA.
Biostatistician: Nancy Johnson, PhD, Hines VA Chicago

REFERENCES


