

To Pump or Not to Pump

First fully described in 1983, intensive insulin therapy attempts to match the levels of insulin in the blood with the physiologic needs of the diabetic patient (1). The results of the Diabetes Control and Complications Trial solidified the importance of this approach to the prevention of microvascular complications of diabetes (2). There are two primary approaches to intensive insulin therapy: 1) multiple daily injections (MDI), and 2) continuous subcutaneous insulin infusion utilizing an external insulin infusion pump (CSII). For the last 10 years, a scientific (and often emotional) debate has existed concerning which approach is superior. The answer is important, as it affects the lifestyle, financial reserves, safety, and glucose control of the diabetic patient.

Subcutaneous insulin does not reproduce the physiological delivery of insulin to the liver and systemic circulation. In humans, insulin is secreted directly into the hepatic portal vein such that the liver is exposed to higher concentrations of insulin compared with the systemic circulation. The liver subsequently removes ~50% of this insulin, thereby lowering the exposure of the peripheral tissues to insulin. This differential insulin exposure has physiological ramifications, resulting in very fine control of intermediary metabolism. In contrast, both CSII and MDI deliver insulin subcutaneously, bypassing the liver and entering the systemic circulation. However, an insulin pump has one unique advantage over insulin injections: the ability to program changes in basal insulin dosage to meet an anticipated increase or decrease in need. This feature can be advantageous in controlling the normal rise in blood glucose concentration before breakfast (i.e., the dawn phenomenon) or preventing anticipated hypoglycemia from exercise or fasting. The ability to set basal profiles has been considered to be the major benefit of the CSII, but a recent study demonstrates that the use of the "dual wave" and "square wave" bolus delivery significantly lowered glucose levels 4 h postprandially (3). This is an algorithm in which the pump delivers a quick bolus and then stretches

out the remaining bolus over a patient-determined number of hours. In theory, this approach more closely mimics the normal insulin delivery of the pancreas in response to food, and may prove to be an additional benefit of CSII in patients with significant postprandial hyperglycemia.

In this issue of *Diabetes Care*, DeVries et al. (4) describe a recent clinical trial comparing MDI (using NPH as the basal insulin and insulin aspart as the acute meal-coverage insulin) to CSII using insulin aspart as both basal and meal-coverage insulin. The results are similar to many previous trials using similar approaches. A recent meta-analysis of published randomized trials concluded that CSII resulted in a small improvement in blood glucose control of ~0.5% HbA_{1c} (5). Although this improvement may result in a decrease in microvascular complications based on the results of the Diabetes Control and Complications Trial (2), the authors conclude that "insulin pump [therapy] should be reserved for those with special problems such as unpredictable hypoglycemia or a marked increase in blood glucose at dawn."

In 2000, insulin glargine was approved by the FDA for use as a basal insulin. This insulin is injected once a day and results in a basal insulin profile that is superior to that with either NPH or ultralente insulin but similar to that with CSII at a constant infusion rate (6). Other studies have demonstrated that insulin glargine reduces the incidence of hypoglycemia compared with NPH, thereby permitting more intensive therapy (7). To date, no long-term studies are available comparing MDI using insulin glargine as the basal insulin with CSII. A short-term study in which a variable CSII was utilized reported less glucose variability compared with fixed-dose insulin glargine (8). Based on the fixed-dose basal insulin profiles obtained with CSII and MDI, very similar overall glucose control might be expected for the majority of patients. If CSII can improve both basal and bolus delivery, what is the current role for CSII in the therapy of the diabetic patient?

To answer this question, the health care provider must first consider the

needs of the individual diabetic patient and whether CSII or MDI better meets these needs. Table 1 lists the major pros and cons that must be considered. The first consideration is cost. Depending upon the manufacturer, an insulin pump costs ~\$5,000. Monthly supplies for pump use exceed \$100. Therefore, health insurance coverage for pump costs is essential for most diabetic patients. Since the costs of insulin glargine and rapid-acting insulin in the pump are similar, the only additional cost to the MDI user is insulin syringes. The health care provider should discuss these costs with the diabetic patient before prescribing CSII.

The second consideration is lifestyle. For some diabetic patients, carrying an insulin pump with them is not a problem, particularly when pagers and cell phones are also frequently carried. Some activities, however, require special care such as contact sports and activities involving water. During these events, either the pump must be removed for a short period of time or provided with increased protection. With "quick disconnect" type infusion sets, the pump can be removed easily for water activities. Individuals who are not willing to make allowances for these inconveniences should not be encouraged to use CSII. On the other hand, CSII users often find that it is easier to vary mealtimes and exercise regimens because they can change the basal rate as needed. In addition, they may be able to better control early morning hyperglycemia (9).

The third consideration is technical expertise. This area has not received much consideration when prescribing CSII. Although MDI does require some

Table 1—Advantages and disadvantages of MDI versus CSII

| Consideration | MDI | CSII |
|-------------------------------|-----|------|
| Cost of therapy | + | ++++ |
| Lifestyle flexibility | ++ | ++ |
| Technical expertise | + | +++ |
| Complications of therapy | + | ++ |
| Glucose normalization | +++ | ++++ |
| Decreased glucose variability | + | +++ |

dexterity and skill in drawing up insulin in the syringe and injecting it correctly, an insulin pump is a complex, sophisticated instrument that requires training in its use. Inappropriate settings on an insulin pump can result in severe, prolonged hypoglycemia with dire consequences. Although severe hypoglycemia can (and does) occur with MDI, injected insulin eventually wanes, whereas pump-infused insulin may continue unabated. For this reason, beginning an insulin pump should always be done under close medical supervision.

The fourth consideration is the different complications encountered with MDI and CSII. Aside from hypoglycemia (which occurs with both approaches), CSII has an increased incidence of diabetic ketoacidosis and subcutaneous skin infections (10). These complications can be avoided by frequent monitoring of blood glucose concentration and changing the insulin delivery catheter every 2–3 days, or as recommended by the manufacturer. The fact that these complications are observed even in very compliant diabetic patients emphasizes the importance of careful health care–provider follow-up.

The fifth consideration is the achievement of normal glucose concentration. Neither CSII nor MDI results in normal glucose concentrations throughout the day and night in the majority of individuals. However, it is possible to reduce the average HbA_{1c} to the top of the normal range. This results in a significant reduction in diabetic complications (2). As reviewed by Pickup et al. (5), CSII is superior to MDI when NPH is used for the basal injection regimen. Studies utilizing insulin glargine in this role are eagerly awaited.

The sixth consideration is the variability of blood glucose concentration throughout the day and especially at night when hypoglycemia can be severe. If CSII is programmed appropriately, this approach is superior to MDI. It is not without risk, however. For example, if the basal insulin pump rate is automatically programmed to increase to cover the dawn phenomenon and this glucose increase does not occur, severe hypoglycemia can occur. Clinical strategies have been developed to guard against this risk (such as waking early to check the blood glucose concentration), but patient cooperation is essential. Another group of patients who may benefit from the

constancy of pump-infused insulin are individuals with labile diabetes who are extremely sensitive to small changes in circulating insulin. The reasons for this sensitivity are complex, but CSII may reduce the frequency of recurrent hyper- and hypoglycemia and thus improve the patient's lifestyle.

The study by DeVries et al. (4) in this issue of *Diabetes Care* emphasizes the difficulty that some individuals encounter with CSII. These authors observed an ~33% dropout rate in spite of the fact that enrollment in their study was voluntary and highly selective. It emphasizes the point that the health care provider should not automatically prescribe CSII because a patient requests it or glucose control is not optimal. The diabetic individual may or may not be similar to the highly selected volunteers who participate in clinical trials. The health care team must discuss the pros and cons of CSII use and be certain that the patient understands the changes in lifestyle that will be necessary. Many patients on CSII become very dependent on their pump to permit their varied lifestyle. If this results in improved compliance and glucose monitoring, then results can be very positive. The challenge for the health care provider is to select the diabetic patients who will really benefit from pump usage. Success with CSII requires record keeping, frequent glucose monitoring, carbohydrate counting, and frequent contact with the health care team (11). Placing individuals on CSII who are unable to master MDI first is a prescription for failure.

In summary, CSII has the advantage of varying the basal insulin delivery to meet anticipated changes in insulin needs. This may be important in a subset of diabetic individuals with variable lifestyles or an exaggerated dawn phenomenon (pre-breakfast rise in blood glucose concentration). For many patients, however, the increase in cost and "hassle" do not offset this feature. For those individuals, MDI using insulin glargine as the basal insulin may prove equally effective. The challenge to the diabetes health care team is to separate the first group from the second group before prescribing insulin pump therapy.

DAVID S. SCHADE, MD¹

VIRGINIA VALENTINE, CNS, BC-ADM, CDE²

From the ¹Division of Endocrinology and Metabolism, Department of Internal Medicine, University of New Mexico School of Medicine, Albuquerque, New Mexico; and the ²Clinical Associate Faculty—University of New Mexico College of Nursing, CEO/Clinical Nurse Specialist – Diabetes Network, Albuquerque, New Mexico.

Address correspondence to David S. Schade, University of New Mexico School of Medicine, Department of Internal Medicine/Division of Endocrinology and Metabolism University of New Mexico Health Sciences Center, 5-ACC, Albuquerque, NM 87131. E-mail: dschade@salud.unm.edu.

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