Are Insulin Pumps Underutilized in Type 1 Diabetes? No

One of the major goals in the treatment of diabetes is to achieve an HbA_{1c} (A1C) <6.5 or 7.0% (depending on which organization's guidelines are used) without an unacceptable incidence of hypoglycemia. This goal has not been achieved in many patients with diabetes. The reasons are diverse and often complex. It is appropriate to ask whether placing more patients with type 1 diabetes on insulin pumps (continuous subcutaneous insulin infusion [CSII]) would achieve this goal and be the best use of limited medical resources. Alternatively, resources could be utilized to purchase insulin analogs, to train additional diabetes educators, to transport patients to diabetes centers, or to purchase improved insulin-delivery devices. Some clinicians believe that increasing the number of type 1 diabetic patients on pumps is the best solution (1,2). It has been estimated that at least 160,000 patients in the U.S. were already utilizing insulin pumps in 2001 and >200,000 worldwide (3). This article will address one specific question, i.e., whether a major effort should be made to increase the number of patients on insulin pumps in order to achieve the above-stated A1C goal.

Determinants of plasma glucose concentration

There are several factors that determine plasma glucose concentration. These include *1*) the carbohydrate composition of food, *2*) the rate of gastric emptying, *3*) the rate of glucose absorption, *4*) the concurrent magnitude of endogenous glucose production, *5*) the concurrent rate of glucose disposal, *6*) the diurnal change in insulin sensitivity, *7*) the activity of counterregulatory hormones, *8*) the change in the magnitude and type of exercise, and *9*) the ambient insulin concentration. It is important to note that most of these factors are not directly under the patient's control. Many of the factors are interrelated, so that altering one may affect the magnitude of the other. Thus, in attempting to normalize plasma glucose concentration in patients with diabetes, the effects of altering a single determinant may result in other physiological changes, making it difficult to accurately predict the results.

It is often not appreciated that insulin delivered with pumps addresses only one determinant of blood glucose concentration (the ambient insulin concentration). For example, if a patient with diabetes using an insulin pump does not accurately match his/her carbohydrate intake to the quantity of insulin administered, then improved blood glucose concentration will not result. The newer "smart pumps" may assist the patient with the math by calculating the dose required based on the patient's own carbohydrate-to-insulin formula, but the patient is responsible for accurately entering the number of grams of carbohydrate to be consumed. All physicians who prescribe insulin pumps have the experience that some patients who request pump therapy do not improve their A1C, in spite of making a significant financial investment in this technology.

Basal versus postprandial glucose concentration

In its simplest form, plasma glucose concentration can be divided into two components, i.e., basal levels and prandial levels. Both of these components significantly contribute to A1C. Both may be associated with hypoglycemia, although in the basal period, it's usually between 3:00 and 4:00 A.M. and, in the prandial state, it's usually 3–4 h postprandially or immediately preprandial. In comparing CSII with multiple daily injection (MDI), each of these approaches has different effects in these periods. CSII can be programmed to deliver insulin in a variable pattern during the meal to more closely mimic a normal insulin curve, although the majority of patients use a bolus dose of insulin very similar to patients using MDI. The reason for this is probably a result of choosing the optimal meal insulin pattern, which is often difficult (4). In contrast to MDI, CSII can also be programmed to provide a variable background rate of basal insulin, most notably in the early morning hours (6:00–8:00 A.M.), when blood glucose concentration tends to increase significantly (usually termed the dawn phenomenon). The mechanism for this glucose rise is still controversial and variable from person to person (5). Since it also may vary in the same individual from day to day, programming a fixed increase in insulin delivery the night before may result in hypoglycemia if the dawn phenomenon is minimal.

Advantages and disadvantages of insulin pumps

Insulin pumps have evolved greatly in the last 20 years, resulting in a decrease in size and an increase in reliability and function. Problems still occur with some pump models and have led to the withdrawal of the pump from the market (6). Because pumps need to be programmed and appropriately refilled, a minimum level of mechanical and technical skill is required. In addition, the expense of purchasing a pump and the required monthly supplies is substantial, usually necessitating medical insurance. Finally, a change in lifestyle is required because each pump patient must accommodate a portable device 24 h/day (7).

The principal advantages of insulin pumps are twofold. First, pumps may provide less variability in insulin levels than injected long-acting insulin. The fact that small amounts of insulin are delivered into the subcutaneous tissue at any one time is preferable to a large injection, which must last several hours. Second, pumps offer the opportunity to vary the rate of insulin infusion during the basal period, as well as surrounding the meal. For example, patients who participate in vigorous exercise can lower the basal rate for several hours before exercise in an effort to avoid hypoglycemia. Advocates of pump use believe that these two advantages will result in less hyperglycemia and a reduction in hypoglycemia.

Advantages and disadvantages of injections

Insulin injections offer advantages not shared with insulin pumps. Most importantly, this method of insulin delivery is less costly than insulin pumps. From data presented by Stephens and Riddle (8) in 2003, 1 month of MDI cost ~$75 compared with ~$250 for CSII (all excluding glucose-monitoring costs). In the U.S., many patients with diabetes do not have medical insurance, and the additional

$100–200/month is prohibitive. Recently, insulin pens have become popular, greatly simplifying the injection of insulin and increasing transport convenience. Improved basal insulins have also become available, with the widespread replacement of NPH insulin by insulin glargine (9). With the recent approval of insulin detemir by the Food and Drug Administration, the variability of basal insulin delivery may continue to decrease (10).

Insulin glargine MDI versus insulin lispro CSII

Because NPH insulin is characterized by excessive variability in absorption, resulting in an increase in both hypoglycemia and hyperglycemia, studies of MDI using NPH versus CSII are no longer relevant (11). Since the widespread availability of insulin glargine, three randomized controlled clinical trials have been published comparing CSII with MDI (using glargine as the basal insulin). The first trial was performed in youths aged 8–21 years and lasted 4 months (12). It demonstrated a small benefit of CSII compared with MDI. The second trial (multicenter) was performed in adults and lasted 10 weeks (13). This cross-over trial also demonstrated a small benefit at one time point. The third trial (two centers) was performed in children aged 1.7–6.1 years and lasted 1 year (14). No difference between MDI and CSII was observed. In a nonrandomized, open, clinical, 1-year trial comparing CSII with MDI, no difference between the therapies was observed in patients chosen for inadequate diabetes control (15). All of these trials suffered from a self-selection bias, a narrowly defined population, and a limited observation period. Therefore, it is difficult to translate these findings to the general type 1 diabetic population. However, in a diabetes center with all patients receiving the same diabetes education, a retrospective review of 103 type 1 diabetic patients (58 on CSII and 45 on MDI) showed that the most recent A1C was similar in both groups (16).

It is often assumed that the delivery of regular and short-acting insulin analogs (e.g., insulin lispro) by CSII results in the least variable absorption of insulin because very small doses of the analog are continuously delivered subcutaneously. Data to support this belief are scarce. In the pharmacokinetic and pharmacodynamic studies of Lepore, there was no difference in the intersubject variability between insulin lispro delivered by CSII and injected insulin glargine throughout a 24-h period (17). In the study by Lauritzen et al. (18), in which regular insulin was delivered by insulin pump bolus, the coefficient of variation within patients for the day-to-day difference ranged from 11 to 35% (18). It is likely that this variability relates to the heterogeneous composition of the subcutaneous tissue.

What is needed?

What is most needed in deciding whether to prescribe insulin pumps for additional patients with type 1 diabetes is a clear and proven description of the necessary requirements for CSII success. Attempts at such a description were made in 2002 by Pickup and Keen (2) in their review of CSII. Unfortunately, this type of documentation has not yet occurred, and a drop-out rate of ~33% can still be observed in selected patients for insulin pump clinical trials (19). Clearly, randomly assigning patients to CSII is not a cost-effective treatment approach. Patients with either excessive hyper- or hypoglycemia can benefit if their primary problem is one of insulin delivery. Frequently, however, the problem is psychosocial or financial, in which case an insulin pump is not the best solution.

Until clear-cut, proven patient screening characteristics are available to practicing physicians, recommendations to significantly increase the number of patients on pumps should not be made. In addition, some strategy needs to be identified to reduce the cost of insulin pumps use so that noninsured patients have a therapeutic choice.

Conclusions

There is little question that insulin pumps can result in improved insulin delivery in some but certainly not all type 1 diabetic patients. As this technology advances and continuous glucose monitoring provides further improvements in the ability of pumps and MDI to match insulin delivery to individual requirements, the need for criteria for payers to begin reimbursement for these products will be critical. Choosing which patients will benefit from CSII is a major challenge to diabetes caregivers. At the present time, a trial-and-error approach is used, which results in a waste of valuable medical resources. Until a screening approach is available that results in a >80% success rate, physicians need to be very cautious as to whom they recommend for pump therapy. Referral to a diabetes educator to work with potential pump patients to help the patient understand all of the lifestyle implications should be standard procedure. All patients considering CSII should go through the process of learning to cover food with insulin accurately and to perform frequent blood glucose monitoring to fine-tune their basal insulin in preparation for starting the pump. If they choose not to undertake CSII, they will still have the benefit of improved MDI therapy. As long as the huge cost disparity between MDI and pump therapy remains, sadly the patient's financial ability to afford CSII remains the most important consideration.

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