Continuous Subcutaneous Insulin Infusion at 25 Years

Evidence base for the expanding use of insulin pump therapy in type 1 diabetes

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Continuous subcutaneous insulin infusion (CSII) is used in selected type 1 diabetic subjects to achieve strict blood glucose control. A quarter of a century after its introduction, world-wide use of CSII is increasing. We review the evidence base that justifies this increase, including effectiveness compared with modern intensified insulin injection regimens and concern about possible complications. Review of controlled trials shows that, in most patients, mean blood glucose concentrations and glycated hemoglobin percentages are either slightly lower or similar on CSII versus multiple insulin injections. However, hypoglycemia is markedly less frequent than during intensive injection therapy. Ketoacidosis occurs at the same rate. Nocturnal glycemic control is improved with insulin pumps, and automatic basal rate changes help to minimize a prebreakfast blood glucose increase (the "dawn phenomenon") often seen with injection therapy. Patients with "brittle" diabetes characterized by recurrent ketoacidosis are often not improved by CSII, although there may be exceptions. We argue that explicit clinical indications for CSII are helpful; we suggest the principal indications for health service or health insurance–funded CSII should include frequent, unpredictable hypoglycemia or a marked dawn phenomenon, which persist after attempts to improve control with intensive insulin injection regimens. In any circumstances, candidates for CSII must be motivated, willing and able to undertake pump therapy, and adequately psychologically stable. Some diabetic patients with well-defined clinical problems are likely to benefit substantially from CSII and should not be denied a trial of the treatment. Their number is relatively small, as would therefore be the demand on funds set aside for this purpose.

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In 1976, we began work developing a new research tool hoped to dramatically improve metabolic control in selected type 1 diabetic subjects, thus enable testing of the links between diabetic control and complications. This technology, continuous subcutaneous insulin infusion (CSII) (often now just called "insulin pump therapy"), uses a portable electromechanical pump to help mimic nondiabetic insulin delivery, infusing short-acting insulin into the subcutaneous tissue at preselected rates—essentially a slow basal rate throughout the 24 h with patient-activated boosts at mealtimes (1–3). Although we originally devised and developed CSII as a research procedure (2,4), its efficacy was quickly confirmed by many groups (5–14), and by the early 1980s, it had been taken up in several countries as an alternative form of routine treatment in a variety of type 1 diabetic patients (15).

A quarter of a century after its introduction, CSII is widely used in clinical practice; there are now estimated (largely from pump sales) to be >200,000 diabetic subjects worldwide using CSII for their everyday treatment, with >130,000 in the U.S. alone (16). However, there are major variations in usage: in some countries, such as the U.K., there are only a few hundred pump users but growing pressure from diabetic patients to increase its availability.

Patient reactions to CSII have been largely enthusiastic and the discontinuation rates low (15,17–19). Good control is achieved without compromising quality of life (20,21). But enthusiasm from some is mixed with uncertainty from others, who are concerned about the possible complications of pump therapy (22) or intensive insulin therapy in general (23).

The advantages and disadvantages of CSII are particularly pertinent in the atmosphere of cost containment and the need for the most appropriate use of expensive technology, which has affected all health care systems in recent decades. The purpose of this article is twofold: to review the evidence base for the expanding use of CSII, in the light of its efficacy and possible side effects, and to initiate a debate about the need for clinical guidelines on the most suitable patients for pump therapy.

Throughout this review, we use the terms "optimized insulin injection regimen" or "intensive insulin injection therapy" to mean modern intensive management of type 1 diabetes, with multiple daily insulin doses given in a basal-bolus mode (with or without an insulin pen), with adjustment according to diet, exercise, and frequent blood glucose self-monitored values and full diabetes educational input. We have not reviewed the use of CSII in type 2 diabetes, where the present evidence base is small.

CONTROLLED TRIALS COMPARING GLYCEMIC CONTROL DURING CSII VERSUS INTENSIVE INSULIN INJECTION REGIMENS

— At least 13 randomized controlled trials have compared CSII

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Abbreviations: CSII, continuous subcutaneous insulin infusion; DCCT, Diabetes Control and Complications Trial.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

with intensified insulin injection regimens (9–11,24–33) and have shown similar mean blood glucose concentrations and glycated hemoglobin percentages in some studies (9,25,27,28) and slightly improved mean glucose and glycated hemoglobin in others (10–11,26,29–33). The number of patients in many of these studies is relatively small (<25 on pump therapy in 10 of the trials), and for this reason, a meta-analysis was performed on the 12 randomized controlled trials of CSII versus multiple injection regimens, where data were reliably extractable (34). This meta-analysis showed a weighted mean difference in blood glucose concentration of 0.9 mmol/l (95% CI 0.5–1.2) and a glycated hemoglobin difference of 0.5% (0.2–0.7) between CSII and optimized injection therapy, favoring CSII. The slightly but significantly better control on CSII was achieved with a 14% average reduction in daily insulin dose: 7.3 units/day (4.1–10.6).

Larger subject numbers have been reported for several nonrandomized controlled trials where CSII was compared with multiple insulin injections (20,35–39). Control (glycated hemoglobin and/or mean blood glucose) was most often significantly improved on CSII (20,35–38) and occasionally similar on CSII and multiple injections (39). In the Diabetes Control and Complications Trial (DCCT), for example, for the 124 subjects who used an insulin pump for >90% of a mean 6.5-year study duration, glycated hemoglobin was 0.2–0.4% lower on CSII than on multiple injections of insulin ($P < 0.001$) (36).

HYPOGLYCEMIA: A POSSIBLE SIDE EFFECT OF CSII OR A CLINICAL INDICATION FOR PUMP THERAPY?

— The notion that pump therapy is associated with severe hypoglycemia might have arisen from early case reports of episodes of hypoglycemic coma during CSII (40) and the fact that the DCCT (36) found that the rate of severe hypoglycemia during CSII was ~2.8 times more frequent than during conventional injection therapy (0.54 vs. 0.19 episodes per patient-year), with similar rates for multiple insulin injections and CSII. Even a recent "evidence-based" review of glycemic control in diabetes concluded that "intensive treatment causes hypoglycemia" (23). However, the DCCT seems to have demonstrated exceptionally high rates of hypoglycemia during pump therapy: the rate was reported at the much lower levels of 0.1 (35), 0.22–0.39 (39), 0.24 (20), and 0.13 (41) episodes per patient-year in other studies with comparable mean blood glucose levels on CSII. Much of the DCCT-associated hypoglycemia may have been due to unfamiliarity with management of tight control because hypoglycemia rates halved during the course of the trial. In fact, the bulk of the evidence suggests that hypoglycemia is markedly less common on CSII than injection therapy. This is even true when comparisons are made with so-called nonoptimized injection regimens (41) where the higher overall blood glucose concentrations might be expected to lower the frequency of hypoglycemia on injections. We found, for example, that the frequency of hypoglycemic coma during CSII in 40 type 1 diabetic patients was less than one-third that of a matched group of type 1 diabetic patients treated by insulin injections (41). Similarly, in a randomized crossover trial of CSII versus insulin injection therapy (42), we found that the number of mild and moderate hypoglycemic episodes (there was no severe hypoglycemia) was reduced by nearly 60% by pump treatment. In another longer-term randomized controlled trial (the Oslo Study) (25), the frequency of hypoglycemic coma was again significantly less on CSII compared with multiple injections.

Notable effects on hypoglycemia also have been described in recent nonrandomized studies. Bode et al. (39) reported on 55 type 1 diabetic subjects who switched to CSII after 1 year on multiple injection therapy; although glycated hemoglobin was similar on the two treatments (7.7 vs. 7.4%, multiple injections vs. CSII), the frequency of severe hypoglycemia was 84% less after 1 year of CSII and 81% less during year two of CSII. Similarly, in another study (20), 25 adolescents chose CSII rather than multiple injections, and even though glycated hemoglobin percentage was lower on pump therapy (8.3 vs. 7.5%, $P = 0.003$), the hypoglycemia rate was reduced by nearly 50%.

The insulin of choice for CSII is now a monomeric insulin such as lispro (Humalog; Eli Lilly, Indianapolis, IN). Insulin aspart (Novo Nordisk, Princeton, NJ) is probably equally effective as a pump insulin (43). Several randomized crossover studies (44–47) comparing lispro with regular short-acting insulin in the pump have shown improved glycated hemoglobin and blood glucose (particularly postprandial) levels with the monomeric insulin. Some studies have shown a reduction in the frequency of hypoglycemia with lispro as the pump insulin (44). It is therefore possible that the differences between insulin injection therapy and CSII would be further emphasized with monomeric insulin in the pump. A recent study comparing CSII using insulin lispro versus intensified injections using lispro and isophane insulin showed lower glycated hemoglobin and mean blood glucose levels on CSII (33).

DIABETIC KETOACIDOSIS

— A few early studies indicated a high rate of ketoacidosis with CSII at some centers (48,49), and some physicians still consider this a serious side effect of CSII (22). But as patients and doctors became more experienced with the technique, the frequency of ketoacidosis decreased (41). Several remediable factors increased the likelihood of ketoacidosis during the first experiences with CSII, including doctor inexperience (poor choice of infusion rates and instructions to patients, etc.), the use of unbuffered insulin (which can cause cannula blockage) (50,51), breakdown of the less reliable pumps of the time (which had no or few alarm systems), cannula dislodgment or leakage (48), and unsuitable patients (poorly compliant, brittle). Patients on CSII have a much smaller subcutaneous depot of insulin than after bolus injections; therefore, ketosis can develop quite quickly if insulin infusion is interrupted (52). Most studies show that with proper education and pump practice, the frequency of ketoacidosis is the same on CSII and injection therapy (20,35,39,41).

MANAGEMENT OF THE DAWN PHENOMENON BY CSII

— A marked rise in the blood glucose concentration before breakfast occurs in many injection-treated type 1 diabetic patients. It has come to be known as the "dawn phenomenon" (53) and is due to a combination of waning of plasma insulin concentrations from the previous evening's delayed-action insulin injection and an increase in insulin resistance

caused by nocturnal surges of growth hormone (54,55). With modern insulin infusion pumps, basal rate changes can be preprogrammed throughout the day, and this allows for an increase during the night, minimizing the dawn blood glucose increase (56).

There are other ways to counteract the dawn phenomenon, such as moving the evening delayed-action insulin from the pre-evening meal to bedtime, thereby extending insulin action (57). However, peaking of intermediate-acting insulin action about 4–6 h after injection produces a higher risk of nocturnal hypoglycemia than with pump therapy; this result was demonstrated in a recent study where substituting nighttime CSII for bedtime isophane reduced the total number of hypoglycemic episodes (58). However, new long-acting insulins, such as glargine (Aventis), made by protein engineering techniques, which are soluble in the vial but precipitate in the subcutaneous tissues, are essentially peakless. The plateau of activity lasting 4–8 h lowers prebreakfast glucose concentrations in comparison with isophane-based regimens (59); it is unclear whether glargine is as effective as CSII in managing the dawn blood glucose increase, and this needs to be tested.

DIABETIC SUBJECTS WHO MAY BE UNSUITABLE FOR CSII

— Patients with severely brittle diabetes (in the sense of a diabetes-disrupted lifestyle with much time off from work or school and multiple admissions to hospital) who suffer from recurrent ketoacidosis and apparent insulin resistance are reported in several studies to be not improved by pump therapy (60–64). Many of these patients are adolescent or young adult females with psychological or social problems (64). They are often suspected of deliberately interfering with treatment (65), which can be difficult to prove, but CSII has offered several opportunities for malefactions, such as dilution of insulin, removal or inversion of batteries, and tampering with infusion cannulas.

Other studies have reported a few patients with brittle diabetes who have benefited from CSII, with reduced hospital admissions and initially lower, but not nearly normalized glycated hemoglobin percentages (66,67). It is not clear why there are brittle diabetic responders and nonresponders; speculations include increased patient confidence from more frequent blood glucose monitoring and more positive interaction with staff (66), and the basal insulin delivery, sufficient to avoid ketoacidosis, is in place without having to rely on patient compliance (67). Nevertheless, Blackett warns that "the selection of such patients should be cautious and based on documentation of glucose monitoring and rapport with the diabetes team" (66).

All candidates for CSII should satisfy certain prerequisites: they should be willing and able to learn about and undertake pump therapy and its associated procedures such as regular blood glucose self-monitoring. Patients who do not meet these requirements or are noncompliant on insulin injection regimens will do badly on pump therapy and in general should not be selected (68). Those with significant psychological problems tend to do worse on CSII, and the demands of pump therapy probably exclude patients with major psychiatric disorders such as psychosis and severe depression. Some diabetic individuals will be physically and emotionally uncomfortable with wearing an external device, which is dependent on mechanical functioning and more obviously advertises a patient's diabetes to the outside world than does injection therapy. There may be concerns too about some contact sports and sexual relationships, and if worries continue after education and counseling, CSII should be avoided in these subjects.

ESTABLISHING GUIDELINES FOR THE USE OF CSII

— The reasons given in published reports for starting patients on CSII as routine therapy have been varied and sometimes (though not always) vague, including poor control and the desire to improve control (How is control measured? How bad is "poor"?); poor control, especially with multiple injections (Does this take into account optimizing education, diet, compliance, etc.?); desire for increased flexibility of eating and activity; pregnancy (Any pregnant diabetic patient?); hypoglycemia unawareness and recurrent hypoglycemia; extreme insulin sensitivity; a severe dawn phenomenon; early complications (Which?); and repeated hospitalizations (For what?).

Clinical guidelines are the first step in making standards of care explicit. Do we need evidence-based consensus guidelines on the indications for a trial of CSII? It might be argued that we do not. Some countries such as the U.S. already have some guidelines: the latest American Diabetes Association Position Statement on CSII (69) offers advice on patient selection (motivation, willingness, capability, etc.) and states that "some clinicians recommend CSII only when three or four daily injections fail to provide euglycemia, [and] others consider CSII indicated for motivated patients whose daily schedule makes conventional therapy less effective." Reimbursement from insurance companies is based on fairly categorical criteria, similar in many cases to those outlined below.

The evidence that we review above suggests that CSII should be more widely available in currently low-use countries. An important way of encouraging this is by establishing guidelines for its most appropriate selective use, essentially by defining the type of clinical problems that are expected to respond to pump therapy. As a framework for discussion, the following indications and contraindications are suggested:

- Evidence from randomized controlled trials indicate that in a large proportion of type 1 diabetic subjects, the glycemic control on CSII is comparable with or only slightly better than that achievable by intensive insulin injection regimens, although it may be quicker and easier to obtain optimal control. Pumps are relatively costly, and special expertise and adequate educational facilities are needed by the medical team to initiate and supervise pump patients. If, then, patients are doing well on optimized multiple insulin injection regimens, insulin pump therapy is not indicated.
- After a 2- to 3-month trial of modern optimized insulin injection therapy (including patient re-education, with attention to blood glucose self-monitoring and injection technique), a trial of CSII is appropriate if poor control persists because of *1*) frequent unpredictable hypoglycemia or 2) a marked dawn blood glucose rise.
- Patients with erratic swings of blood glucose concentration or an erratic lifestyle with delayed or missed meals and unpredictable activity will fall into the first category when attempts to improve control with insulin injections lead to frequent hypoglycemia. It is possible

that patients with unpredictable swings in blood glucose short of hypoglycemia, but persisting on optimized insulin injection regimens, also should be offered a trial of CSII.

- CSII is an effective means of managing diabetes during pregnancy (70–72), but these patients, as a group, are not better controlled than during multiple injections. The few individual pregnant diabetic patients who fail to achieve excellent control with optimized insulin injection therapy should be considered for a trial of CSII.

What of patients who are satisfactorily controlled on insulin injections but who simply prefer CSII as their form of optimized insulin therapy. It may be noted that many diabetic patients prefer the convenience of insulin pens for optimized injection therapy. Even though (unlike pumps) there is no evidence that pens improve diabetic control, these devices are accepted in many parts of the (Western) world as routine therapy where patients prefer them because they carry little if any additional cost implications. If funding is secured for CSII from private sources or health insurance, we consider that such patients should be considered for CSII. Even if private funding is available, these patients should also meet the prerequisites for CSII shown below, and proper medical supervision should be in place.

We are aware our suggested indications are open to dispute and debate and are short on definition, e.g., how severe and how frequent is hypoglycemia to be and what magnitude of dawn blood glucose increase defines an indication for pump therapy? We welcome opinion and discussion.

CONCLUSIONS — The evidence base suggests that the expanding use of CSII is justified. The unwillingness to fund pump therapy in some countries arises in part from the erroneous belief that it is indicated for a large proportion of type 1 diabetic patients, which would open a floodgate of cost implications. If we can reach agreement about some simple clinical guidelines for CSII, those who stand to benefit could be greatly helped at an affordable cost. Finally, we recommend a continued audit of the clinical reasons for starting pump therapy, its metabolic effectiveness, possible side effects, impact on long-term tissue complications, quality of life, and patient choice of treatment methods in type 1 diabetes.

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