Are Insulin Pumps Underutilized in Type 1 Diabetes? Yes

Continuous subcutaneous insulin infusion (CSII), popularly called insulin pump therapy, has evolved from its invention in the 1970s as an experimental treatment designed to test the relationship between glycemic control and diabetic tissue complications (1) to its present status as a routine therapy for selected type 1 diabetic patients (2). However, the use of insulin pump therapy varies markedly throughout the world; there are some notable high-use countries, e.g., the U.S. and Israel, where it is estimated that ~20% of type 1 diabetic patients use CSII (manufacturers' estimates), whereas in other countries, such as the U.K. and Denmark, ~1% use pump therapy (3).

The reasons for this variation include the availability of financial resources and health care professionals to supervise CSII and a lack of knowledge on the effectiveness of CSII (3), but there is also disagreement on which diabetic subjects should be treated with CSII, as evidenced by both the different intercountry usage and the large number of reasons for starting insulin pump therapy (4–6).

As noted by Schade and Valentine (7), "the challenge for the health care provider is to select the diabetic patients who will really benefit from pump usage." What proportion and what types of type 1 diabetic patients should then be offered a trial of CSII on clinical grounds alone, leaving aside the legitimate issues of supply on the basis of patient preference and restrictions due to availability of funding and staffing? I shall argue that the target proportion best treated by CSII, or offered a trial of CSII, can be derived from an estimate of the effectiveness of this therapy compared with the best insulin injection treatment for particular clinical problems in type 1 diabetes.

Most current guidelines (4,6) or reviews of the evidence base on CSII (2) do not take into account recent studies on the effectiveness of pump therapy in the putative target groups of hypoglycemia-prone diabetes and the worst controlled subjects or the possible impact of recently introduced long-acting insulin analogs on the quality of control achievable with injection therapy. The efficacy of CSII in the most appropriate groups of patients is also a key determinant of cost effectiveness, the estimates of which are limited (8).

The problem of severe hypoglycemia

Reduction of severe hypoglycemia (where third-party assistance is required for resuscitative measures) in type 1 diabetes was first identified in the mid-1980s, either with matched groups of injection- or pump-treated type 1 diabetic subjects (9) or in a randomized controlled trial of multiple insulin injection (MDI) therapy (and nonoptimized injection therapy) versus CSII (the Oslo Study [10]). Many subsequent studies have confirmed the hypoglycemia-reducing effect of insulin pumps (2,11–13), with typical reductions in frequency of severe hypoglycemia of ~70% compared with MDI.

The clinical impact of this beneficial effect was undervalued until recently because of the untypically high frequency of severe hypoglycemia reported in the pump-treated subjects in the Diabetes Control and Complications Trial (DCCT) (0.5 vs. ~0.1–0.25 episodes/patient-year in other pump studies) (14). The explanation for this discrepancy is unclear but may relate to a large number of centers in the DCCT that were using pump therapy for the first time.

Frequency estimation for severe hypoglycemia

Estimating the proportion of type 1 diabetic subjects with severe hypoglycemia is difficult because it critically depends on patient selection. Many factors influence hypoglycemia frequency (15,16), including the definition of severe hypoglycemia (e.g., requiring any assistance or, specifically intravenous glucose/glucagon injection), the type of treatment (intensive versus conventional regimens), prevailing glycemic level, diabetes duration, concomitant drug usage, alcohol intake, presence of autonomic neuropathy and renal disease, smoking, educational level, and history of previous hypoglycemia and hypoglycemia awareness.

A further issue is the judgement about what frequency of hypoglycemia is disabling. Some guidelines for insulin pump therapy (6) define this as the "repeated and unpredictable occurrence" of hypoglycemia without stipulating what "repeated" means. A recent cross-sectional study of 1,076 consecutive adult type 1 diabetic patients treated according to modern guidelines at four centers in the U.K. and Denmark is informative in this respect (16). As many as 21% had two or more severe hypoglycemic episodes in the previous year, as compared with a mean of 13% suffering severe hypoglycemia in the previous year over a 12-year study of an intensified insulin program in Germany (17). However, the definition of hypoglycemia here was the requirment of intravenous glucose or glucagon injection, so the frequency of hypoglycemia requiring any assistance would be higher. Yet the distribution of severe hypoglycemia in the type 1 diabetic population is extremely skewed, with ~5% of patients having 70% of all episodes (16). This therefore represents a reasonable minimum target group, although many more might suffer hypoglycemia, which is disabling for them.

The impact of long-acting insulin analogs on severe hypoglycemia

There is no strong evidence that using glargine or detemir insulins (with their flatter profile and improved predictability), instead of isophane-based regimens, will reduce the frequency of severe hypoglycemia (18). Although minor hypoglycemia during the night is less with long-acting analogs, there is no difference in the rate of severe hypoglycemia when an MDI regimen using isophane as the basal insulin is compared with either glargine-based (18,19) or detemir-based (20–22) injection regimens. Severe hypoglycemia over extended periods has not been well studied in randomized trials directly comparing glargine-based regimens and CSII because of the relatively short-term nature of the studies (23–25). However, since severe hypoglycemia does not appear, based on current evidence, to be reduced with MDI, based on long-acting insulin analogs compared with isophane regimens, the use of CSII to improve hypoglycemia frequency during MDI is still justified.

The problem of hyperglycemia and elevated glycated HbA_{1c} on MDI

Until recently, the belief was that the difference in average glycemia achievable on pump therapy was relatively small compared with MDI (2,6,26). For example, a meta-analysis of 12 randomized controlled trials indicated that glycemic control on pump therapy was slightly but significantly better than on MDI, with a difference in HbA_{1c} (A1C) of 0.5% and mean blood glucose concentration of 1 mmol/l (26). However, recent work from several groups, including a pooled analysis of randomized controlled trials, has shown that the fall in A1C on switching type 1 diabetic subjects who have failed to achieve good control on MDI to CSII is directly proportional to the initial A1C on MDI (27–29). Thus, the best improvement is seen in the worst-controlled subjects (who are the likely candidates for pump therapy), a fact that was obscured in previous trials of unselected, general type 1 diabetic patients without clinical problems (26). When, for example, the starting A1C is 10% on MDI, the fall in A1C on switching to CSII is likely to be ~2% but, in a relatively well-controlled subject with an A1C of 7%, the difference in A1C could be <0.5% (28).

Frequency estimation for markedly elevated A1C

A good estimate of the quality of control that is achievable on MDI comes from studies where therapy combines basal/bolus insulin injection, frequent blood glucose self-monitoring, dietary advice, insulin dosage adjustment according to meal composition and size, structured patient education, and adequate contact and advice from health care professionals. The level at which glycemia is so elevated that CSII should be considered is debatable, but, as an example, I have calculated the mean percentage of subjects with an A1C >9.5% from the distribution of reported values in a number of trials and surveys describing the injection regimen as MDI (12,24,28,30) or as "intensified," with a description of dosage-adjusted basal-bolus therapy in the methods (13,17,31) as 15%. This estimate needs to be confirmed by a more extensive survey of the literature, but I suggest that this would represent a reasonable first estimate of the target population for a trial of pump therapy, i.e., the ~15% who remain very poorly controlled (elevated A1C) after best attempts with MDI.

The impact of glargine and detemir on hyperglycemia

Though there may be lowered fasting blood glucose concentrations, overall glycemia as measured by A1C is usually not improved by glargine or detemir compared with NPH-based injection regimens in type 1 diabetes (18,19,21,22,32). In studies comparing glargine with pump therapy, A1C or fructosamine values were improved on CSII versus glargine (23,24,32), but in relatively well-controlled subjects, A1C percentages were similar (25). Thus, the evidence to date indicates that long-acting insulin analog–based injection regimens are not as effective as pump therapy in lowering glycemia in most poorly controlled type 1 diabetic patients, and the target group with elevated A1C on injections suitable for a trial of CSII will remain at ~15%.

The syndrome of hyperglycemia, blood glucose variability, and unpredictable hypoglycemia

Who are the patients who remain hyperglycemic on MDI? It might be thought that elevated blood glucose concentrations can be obviated by increasing the insulin dosage. However, the patients with the highest A1C during MDI also have the widest swings in blood glucose levels, and it is probable that they (or their health care professionals) resist attempts to lower the mean glucose level for fear of inducing hypoglycemia (28). This explains why many patients who are considered hypoglycemia prone have actually had few recent serious hypoglycemic episodes (30) but are characterized by frequent, unpredictable glycemic oscillations and episodes of biochemical or moderate hypoglycemia. They usually maintain a high A1C. Both within- and between-day blood glucose variability is significantly improved by switching from insulin injections to pump therapy (28,30).

We do not know if such patients with variable control always belong to the same population as those who are hyperglycemic on best attempts with injection therapy, and glycemic predictability (if not A1C) is often improved by glargine and detemir (20–22). However, it seems likely that, after a period of attempting to improve control with MDI, at least 15% of type 1 diabetic patients are markedly uncontrolled, with either an elevated A1C or glycemic variability or both, and are at least candidates for a trial of CSII.

The problem of the dawn phenomenon

The dawn phenomenon refers to the rise in blood glucose concentration in some diabetic patients occurring in the few hours before breakfast, without preceding hypoglycemia; it is thought to be due to a combination of insulin resistance caused by surges in growth hormone during the night and insulin deficiency caused by waning of the effects of the preceding evening's insulin injection (33). Increasing the evening long-acting insulin dose or delaying its injection to bedtime to extend action are useful strategies for treating the dawn phenomenon, but both can lead to nocturnal hypoglycemia. The phenomenon can be successfully managed by CSII because the basal insulin infusion rate can be preset to increase during the dawn hours (33).

The frequency of the dawn phenomenon during MDI is difficult to judge. Relatively few patients are referred to our specialist pump clinic because of a marked dawn phenomenon and probably many can now be managed by glargine or detemir regimens, which are often very effective at lowering fasting blood glucose without increasing hypoglycemia (18–22). Moreover, the long-term clinical consequences of a marked dawn phenomenon are unclear. A mean fasting plasma glucose concentration as high as 10 mmol/l was associated with a mean A1C of only 7.5% in one study (19). Probably, then, there will be relatively few patients with the dawn phenomenon who will need to be treated by pump therapy.

Patient choice and patient suitability

If patients were allowed to choose insulin pump therapy as their routine treatment, without respect to cost or whether there was a clinical problem with their diabetes control on injection therapy, there would undoubtedly be a large enrollment increase. Quality of life is reported to be better during pump therapy than MDI (13), and in a survey in the U.S. in 2000, more than half of the health care diabetes specialists who themselves have type 1 diabetes were being treated by pump therapy (34). There are probably more now. There is need for much more research on the degree of improvement in lifestyle afforded by insulin pumps, but here I restrict estimates of individuals who might be treated by CSII to the clinical problems outlined above, which also might form an improved basis for future cost-effectiveness analyses.

Conclusions

There are some 5% of type 1 diabetic subjects treated by MDI with severe, recurrent hypoglycemia. At least another 5% suffer severe hypoglycemia at such a frequency that it is markedly disabling to them. I estimate that ~15% of type 1 diabetic subjects on MDI have the syndrome of markedly elevated A1C and wide swings in blood glucose concentration, often with unpredictable, moderate (nonsevere) hypoglycemia. A small percentage will have the dawn phenomenon. These clinical problems are at least as important in children as adults (35). According to present evidence, the proportion of subjects with severe hypoglycemia or unacceptable hyperglycemia who are improved by regimens using new long-acting insulin analogs is likely to be small.

Some patients are known to be unsuitable for insulin pump treatment (2) because they are unable to perform pump procedures or are psychologically unsuitable or simply decline this treatment option and prefer MDI. Even using the most conservative estimate that this number is as much as one-quarter of those with the above clinical problems, a reasonable minimum target for those type 1 diabetic patients who should be offered a trial of insulin pump therapy is therefore ~15–20% of type 1 diabetic subjects. This a percentage of patients similar to that already treated as such in the U.S. and some other countries.

It must be emphasized that most health care professionals recommend a sequential approach to selecting patients for CSII on clinical grounds, with best efforts first being applied to MDI (with long-acting insulin analogs if necessary) and with appropriate education and diet before offering a trial of CSII to those who fail to achieve satisfactory glycemic control on such a regimen. I strongly recommend that this practice continue and that only after MDI has been tried and hypoglycemia and/or an elevated A1C persist should a trial of CSII be considered.

I do not underestimate the organizational, financial, staffing, and political challenges that that must be faced in meeting this target in many countries or the need for continuing research into quality of life, cost effectiveness, and other possible benefits of CSII. Some countries may not be able to achieve this suggested level of pump usage in the near future for several reasons, but that should not influence our estimates of those who might be best treated by CSII on clinical grounds. Neither do we know how changes in pump technology in the coming decades will influence these difficulties: smaller and cheaper pumps may make pump usage more widespread but more sophisticated and expensive devices may not.

I do not take "many" to mean "most" and do not believe, based on current evidence, that the majority of type 1 diabetic patients should be treated by CSII. However, there is a good evidence base for the substantial minority (the many) who cannot be well treated by MDI to be so managed.

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