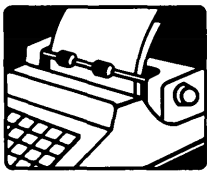
Editorial



Type I Diabetes . . . Regimens, Targets, and Caveats

The control of glycemia in patients with insulin-dependent diabetes mellitus (IDDM) has bedeviled physicians since the introduction of insulin therapy in 1922. Prolongation of life permitted by insulin allowed the emergence of the chronic degenerative complications of diabetes, including microangiopathy involving the eyes and kidneys, in particular, neuropathy; and accelerated atherosclerosis. As has been discussed on these pages in the past, the weight of currently available scientific evidence strongly suggests that the microangiopathic and neurologic complications of diabetes arise as a consequence of, or are in large part influenced by, the metabolic derangements that characterize the diabetic state.[1–3] This has stimulated physicians to attempt to develop therapeutic approaches that will improve glycemic control, in the hope that this would lessen the risk of development of these complications. As a consequence, during the past few years there has been a marked improvement in our ability to effectively control glycemia in patients with IDDM. A number of advances have contributed to this, and DIABETES CARE has served as an important forum for their presentation. Perhaps the most important of these advances is the development of patient self-monitoring of blood glucose (SMBG) as a practical clinical tool, thus permitting the definition of treatment targets near the physiologic range, and providing the ability to document the level of glycemia that is attained during ordinary life.[4–11] Moreover, the routine use of SMBG permits the development and implementation of a plan designed to achieve those treatment targets.[12,13] Studies of appropriate waveforms for automated intravenous insulin delivery and the development of portable infusion pumps for subcutaneous insulin delivery have not only provided a new approach to insulin therapy but have contributed to a renewed interest in insulin availability and the design of treatment regimens.[14–20] These and other studies[21,22] have served to emphasize the distinction between basal insulin availability and meal-related insulin availability. Additional studies elucidated the "dawn phenomenon" of increased basal insulin requirement on awakening and before consumption of breakfast.[23–25] Other recent advances, which have contributed to our understanding and use of insulin, have been the development of assays for circulating free insulin, permitting measurement of insulin levels in insulin-treated patients,[26] and for glycosylated hemoglobin, permitting documentation of average glycemic control attained over several weeks.[27,28]

The use of mechanical devices to deliver insulin has received particular attention as a method to improve glycemic control in IDDM. Indeed, in studies of ambulatory subjects treated for 6–12 mo or more, continuous subcutaneous insulin infusion (CSII) has been shown to result in near-normalization of glucose control,[29,30] with consequent improvement in functional changes in eyes,[31,32] kidneys,[31,33] and nerves.[34] A critical question that has emerged is whether infusion devices uniquely permit the attainment of near-normalization of glycemia or whether other insulin regimens administered by conventional syringe and needle, if properly designed, also might result in such near-normalization. Unfortunately, many of the early studies compared control achieved with CSII to that attained with a suboptimal nonphysiologic insulin regimen. Moreover, with the introduction of CSII patients also received increased attention and education, renewed dietary instruction, and began self-monitoring of blood glucose.

A number of more recent studies have compared CSII with "intensified" conventional therapy. Insulin regimens were designed to be more physiologic (i.e., to provide basal insulin availability and meal-related increased insulin availability), and also provided patients with comparable degrees of attention, education, and dietary advice, as well as incorporating the use of SMBG. These studies have included both short-term in-hospital comparisons[35–37] and intermediate-term outpatient comparisons, entailing a crossover design.[35,37–40] Two additional studies are reported in this issue of DIABETES CARE.[41,42]

The results of these regimen comparison studies have not been uniform. All three studies involving inpatient comparisons have demonstrated equivalent glycemic control with both CSII and the intensified conventional regimens with

which it was compared.[35–37] In contrast, in three of the seven outpatient studies, comparable glycemic control was achieved with both CSII and the intensified conventional regimens with which it was compared,[39–41] while in the other four studies better control was demonstrated with CSII.[35,37,38,42] It seems worthwhile to examine these studies in search of an explanation for the apparent divergent results.

The inpatient studies comparing CSII and intensified conventional therapy (ICT) have been of only a few days duration. The controlled environment of the hospital, with fixed activity schedule, meals prepared according to precise prescription, and freedom from the stresses of daily living, clearly facilitates the attainment of the excellent control achieved with both CSII and ICT in the reports of Champion et al.[35] and Nathan et al.[37] An additional factor in the study by Rizza et al.[36] was that near-normalization of glycemia was attained using a glucose-sensor-controlled automated insulin infusion system (Biostator, Miles Laboratories, Elkhart, Indiana) and maintained for a few days with CSII and ICT.

The differing results of the outpatient comparison studies may be explained, in part, by differences in the degree and intensity of the conventional regimens. Although it is impossible to determine the extent and effectiveness of patient education, design of the dietary regimen and instruction therein, support structure and degree of contact with the management team, and other such variables in the reported studies, some relevant differences in the self-monitoring approaches employed are evident in the descriptions of the treatment programs used (Table 1). These include differences in the target level of glycemia aimed for, the frequency of blood glucose self-monitoring, and whether or not patients were trained in making adjustments in the basic insulin dosage and/or in the use of supplemental insulin to correct hyperglycemia above a predetermined level. Of note,

TABLE 1
Summary of outpatient comparative studies of CSII versus "intensified" conventional therapy (ICT)

Study	N	"Intensified" conventional regimen(s)	Simplified results summary	Target level of glycemia	Frequency of self-monitoring	Use of patient adjustments and supplements
Champion et al.[35]	8	AC-B: R/I AC-S: R/I	CSII > ICT CSII: NN ICT: Subopt	"Normalize" PC < 150	2/day (fasting and HS)	No
Barbosa et al.[38]*	12	Varied†	CSII > ICT Both: Subopt	FPG: 60–100 AC: <110 1 h PC: <170	2–5/day (AC and PC)	Supplements only
Reeves et al.[39]	10	(1)AC-B: R/I AC-S: R/I	CSII=ICT_1=ICT_2	FPG: 60–90	4–7/day	Both adjustments and supplements
		(2)AC-B: R/UL AC-L: R AC-S: R/UL (HS: R)	All: NN	AC: 60–105 2 h PC: 60–120	(AC and PC)	
Schiffrin et al.[40]	16	AC-B: R AC-L: R AC-S: R HS: I	CSII=ICT Both: NN	FPG: 60/90 1 h PC: <140	7/day decreasing to 4–7/day (AC and PC)	Both adjustments and supplements
Nathan et al.[37]	5	Varied‡	CSII > ICT CSII: NN ICT: Subopt	FPG: <90 PC: <150	4/day (half PC)	Supplements only
Calabrese et al.[41]	5	AC-B: R AC-L: R AC-S: R/I	CSII=ICT Both: Subopt	"Best possible"	7/day every 3rd day	Not specified
Home et al.[42]	10	AC-B: R AC-L: R AC-S: R/UL	CSII > ICT CSII: NN ICT: Subopt	FPG, AC, PC all 72–144	2/day routine 7/day twice weekly 4/day after adjustment	No

Abbreviations used: AC, preprandial; B, breakfast; L, lunch; S, supper; HS, bedtime; R, regular insulin; I, intermediate-acting insulin; UL, ultralente insulin; >, better than; =, equivalent results; NN, near-normalization of glycemic control; subopt, suboptimal glycemic control; FPG, fasting plasma glucose; PC, postprandial.

* Four of Barbosa's patients had very labile ("brittle") diabetes, and the other eight were renal transplant recipients treated with steroids.

† Seven of Barbosa's patients were treated with R/I twice daily (AC-B and AC-S); four were treated with R AC-B and AC-L, and with R/I AC-S; one was treated with R AC-B, AC-L, and AC-S and with I HS.

‡ Two of Nathan's patients were treated with AC-B: R/I, AC-L: R, AC-S: R/I; two were treated with AC-B: R/I, AC-L: R, AC-S: R, HS: I; one subject was treated with R AC-B, AC-L, and AC-S, accompanied by once-daily I or UL on two different comparisons.

the two studies in which near-normalization of glycemic control was achieved with ICT (Reeves et al.[39] and Schiffrin et al.[40]) used the most stringent glucose targets and the highest frequency of SMBG, and were the only studies which explicitly stated that patients were taught both insulin dose adjustments and use of supplemental insulin. It may very well be that these factors are of greater importance when using ICT than when using CSII. Another factor complicating the study of Home et al.,[42] which may partially explain their relative lack of success with ICT, was that they admittedly were inexperienced with the use of the ultralente-based ICT program at the outset of their study. Thus, their patients showed deterioration of control when that regimen was begun and they never fully caught up during the 10-wk study period, although the trend was clearly in that direction since mean blood glucose levels were not significantly different at the end of the study when CSII and ICT were compared. Now that they have greater experience with this regimen, these investigators are performing a similar study with an additional group of patients (personal communication). Finally, as mentioned in a footnote in Table 1, it should also be appreciated that the patients studied by Barbosa et al.[38] are not comparable to those who participated in the other studies. Barbosa et al. specifically studied patients with very labile diabetes and patients who had received kidney transplants and were being treated with steroids. This difference in study population certainly accounts in large part for the suboptimal control demonstrated with CSII and to a greater degree with ICT.

The study by Calabrese et al.[41] raises another issue, namely, how regimens should be compared. In that study, suboptimal control was achieved with both regimens. Although there were no differences in glycemic control between CSII and ICT based on data collected in an ambulatory free-living state, glycemic control was better with CSII when assessed in the hospital. It may be that with the introduction of the controlled environment of the hospital, better control was more rapidly attained with CSII than with ICT, and that this was more dramatic in the study of Calabrese et al. because the prevailing level of glycemic control at home was less in that study than in most of the other reports. It should be noted, however, that others observed differences between the apparent level of glycemic control measured at home versus that measured in the hospital, for the same regimen at the same time. An example is the study of Reeves et al.[39] In that report, the investigators attributed the differences to the different basis by which values were calculated. Another possibility is that control was actually better on the days patients were hospitalized and the environment controlled. Although inpatient evaluations permit more detailed measurements to be made, they demonstrate the best control achieved and may not be fully representative of the real world situation. Both types of evaluation seem desirable.

It is evident from Table 1 that a variety of different insulin regimens have been used as ICT. A commonality of all those listed is that they involve multiple components of insulin action, each regimen containing at least four components. All these regimens are designed to provide one component for each major meal and a component to provide continuing insulin availability in the basal state overnight. In this respect, these regimens are designed to provide insulin availability in a more or less physiologic manner. Virtually all these regimens have been demonstrated to be capable of achieving near-normalization of glycemia in the context of an intensified program of diabetes management in C-peptide-deficient patients with IDDM. In contrast, in such patients near-normalization is not demonstrable with nonphysiologic regimens, such as once-daily insulin (even as a mixture of regular and intermediate-acting insulin) or twice-daily intermediate-acting insulin.

A study by Daneman et al.[43] elsewhere in this issue of DIABETES CARE reports that when one versus two daily injections are compared in a group of subjects who monitored their diabetes with urine testing, glycemic control was comparable in both groups. Yet despite effort and attention, glycemic control was only fair to poor in both groups. This is similar to other reports[44,45] that have also demonstrated that equal degrees of poor control are achievable with nonphysiologic regimens monitored by urine testing. This is in stark contrast to the control achieved in any of the reports listed in Table 1, all of which used SMBG. It emphasizes again the fact that urine monitoring is too crude if excellent control is desired, because urine testing is both semiquantitative and inaccurate. Moreover, even continuous aglycosuria indicates only that glycemia is below renal threshold, a less than optimal target.

An article by Schiffrin and Belmonte[46] also in this issue is particularly instructive in terms of the use of SMBG. That article reports further observations on the patients reported earlier and cited above,[40] as well as others reported earlier in whom daytime preprandial conventional injections were combined with an overnight basal infusion by CSII.[47] In the current study, it is demonstrated that the maintenance of near-normalization of glycemia requires the use of SMBG four or more times daily, in contrast to deterioration of control when SMBG was performed but twice daily. Schiffrin and Belmonte emphasize the dual purpose of SMBG, both to monitor glucose levels and to be used in dosage adjustment. They note that SMBG is indispensable in maintaining excellent control. Inherent in their article and the successful reports listed in Table 1 is that excellent glycemic control also required that glucose targets are defined and are near normal, as well as measured and used to adjust insulin dosage.

A few caveats must be noted. Foremost is that vigilence must be exerted to avoid nocturnal hypoglycemia. Since a subtle physiologic glucose nadir occurs around 3:00 to 4:00 a.m. even in nondiabetic individuals, and since the dawn phenomenon[23–25] may result in disproportionately high levels of glycemia before breakfast, caution must be used in adjusting the overnight component of insulin in both CSII and ICT programs. Our recommendation is that a regimen not be altered on the basis of prebreakfast values without first verifying that hypoglycemia is not present at 3:00 to 4:00 a.m.[13,48] The potential dangers of nocturnal hypoglycemia

have been emphasized in a recent commentary by Unger.[49] These dangers are particularly present in patients who have hypoglycemic unawareness and/or deficiencies in counterregulatory responsiveness.[50,51] Pregnant women may be more prone to nocturnal hypoglycemia than nonpregnant individuals, due to continuing consumption of glucose by the conceptus. Would that we could just precisely adjust insulin infusion rates or doses to always avoid the risk of hypoglycemia and yet still achieve good to excellent glycemic control.

Another caveat to be aware of is that with the institution of improved glycemic control many patients feel quite uncomfortable and may develop symptoms of hypoglycemia with normal concentrations of plasma glucose. This is accompanied by a measurable counterregulatory response[52] and may be accounted for by an influence of chronically elevated plasma glucose in repressing glucose transport capacity of the blood-brain barrier, a phenomenon recently demonstrated in rats.[53] Health professionals and patients should be aware of the symptomatic discomfort that predictably occurs with establishment of markedly improved glycemic control, and patients should be assured that it is a transient phenomenon lasting between several days and a fortnight. After adaptation to normoglycemia, these symptoms abate and indeed patients usually feel better than they did in the face of chronic hyperglycemia.

Physicians should be aware that established clinical complications (retinopathy, nephropathy) apparently do not improve with the institution of markedly improved glycemic control with CSII or ICT.[54] It is not likely that structural changes would improve, although, as noted earlier, functional alterations do.[31–34] Indeed, there is evidence that established retinopathy may worsen when patients with very poor control undergo vigorous treatment of glycemia.[55]

Another caveat is that there are distinct differences in the degree of flexibility in life-style possible with the various ICT regimens, as well as with CSII. Any regimen that uses preprandial regular insulin (either as an injection or a bolus) permits flexibility in meal size, with the insulin dose varying with the anticipated carbohydrate or calorie content of the meal. Indeed, in this issue Hamet et al. describe their experience with a CSII program in which the magnitude of preprandial boluses was based solely on meal content.[56] Although this is an extreme example of application of this principle in that prevailing levels of preprandial glycemia were not considered, it does serve to emphasize the principle of flexibility of meal content and the need for patients to be aware of food composition. Further flexibility is possible with CSII and with those ICT regimens that provide a background of basal insulinemia during the course of the day as well as the night (e.g., ultralente insulin). In this circumstance, there can be considerable flexibility in meal timing (which is helpful for shift workers or those with varying schedules) and even omission of a meal with omission of the preprandial regular insulin bolus or dose. This flexibility in timing is not possible with the multiple-dose ICT regimen in which regular insulin is administered before meals and intermediate-acting insulin is administered at bedtime. Indeed, with this regimen Schiffrin et al. noted that delay of a meal and hence delay of an insulin dose resulted in hyperglycemia outside the target range, since sustained insulin availability was absent.[40]

On the other hand, ICT regimens using ultralente insulin have problems of their own. Their use is predicated on the assumption that the action of ultralente insulin is prolonged and relatively peakless. In our clinical experience with this insulin, this is the case in only about 50% of patients. The other patients manifest a peak of action, of greater or lesser degree, at a variable time after administration of ultralente insulin. This peak time is generally fairly consistent for any individual patient, and usually appears to occur either 12–15 or 22–28 h after administration. A consistent peak can be both contended with and taken advantage of. Unfortunately, the dissolution of ultralente insulin crystals is a variable that may contribute to variable insulin absorption. Binder has shown that the coefficient of variation of absorption of ultralente insulin is 25–35%.[57] Based on a predicted 36-h period of absorption, this would mean that the size of the ultralente depot at any one time varies between 90% and 240% of the daily dose, a veritable time bomb which if released could cause sustained hypoglycemia, a problem encountered in patients treated with ultralente insulin.

The prolonged period of absorption of ultralente insulin accounts for another important point about use of this insulin, namely, that it will take approximately 4 days to see the effect of a dosage change. This has resulted in a suggestion by Turner that initiation of an ultralente insulin program be with a loading dose, threefold the size of the predicted daily dose.[58] Although this is not unreasonable based on the known pharmacology of ultralente insulin, most clinicians are too timid to institute this practice.

The above type of pharmacokinetic considerations may provide unique advantages to CSII. The shorter the time period of insulin absorption, the less variation there will be in time course of action and in depot size.[57] Continuing absorption of basal insulin means that only the preprandial boluses contribute to the subcutaneous depot in patients with CSII, thus minimizing an important variable in insulin action, and perhaps limiting the risk of exercise-induced hypoglycemia.

A final caveat concerning CSII is related to the programmability featured by several new infusion pumps. This programmability of basal rate permits decreasing the rate during sleep to avoid nocturnal hypoglycemia. It also permits automatically increasing the basal rate before awakening, in an attempt to avert the dawn phenomenon.[23–25] Although of theoretical advantage, the practical considerations of such programming have not been thoroughly explored and reported. Particularly in view of the deaths reported in CSII patients,[59] it would seem prudent to recommend that practicing physicians not use the automatic basal rate increment feature until clinical investigation clearly has established its efficacy and appropriate use.

In summary, both CSII and ICT, if appropriately used, offer the possibility of achieving excellent glycemic control. It may be easier to achieve such control with CSII, which

also may have advantages in terms of the pharmacokinetics of insulin availability. CSII and some ICT regimens offer the patient flexibility of meal size and meal timing, including the possibility of omitting a meal, if so desired. Successful application of these regimens, particularly ICT, requires careful attention to all aspects of diabetes management, the clear definition of therapeutic targets, regular use of SMBG (probably four or more samples daily), and patient-initiated adjustments in insulin dosage and use of supplemental insulin. Vigilence must be exerted to avoid nocturnal hypoglycemia. The improvement in glycemic control achieved with intensive approaches has been demonstrated to improve functional alterations associated with the diabetic state,[31–34] and may offer the promise of decreasing the risk of chronic complications of diabetes,[1–3] but should not be expected to reverse established complications.[54] The state of the art is rapidly changing. In the next few years, further advances will result in improvement in our ability to achieve excellent glycemic control while lessening the attendant risks thereof.

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