The Use of Insulin Pump Therapy in the Pediatric Age Group

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Abstract
Diabetic children and their caregivers face the never-ceasing challenge of maintaining blood glucose levels as close as possible to the normal range so as to prevent or delay long-term micro- and macrovascular complications, to minimize the risk of severe hypoglycemic episodes, and to improve quality of life. Continuous subcutaneous insulin infusion (CSII) therapy represents a treatment option that can aid in achieving these goals. Granted that insulin secretor responses to physiological stimuli are complex and difficult to duplicate, CSII is the most physiological method of insulin delivery currently available, simulating the pattern of insulin secretion with a continuous adjustable ‘basal’ delivery and superimposed mealtime ‘boluses’. CSII offers greater flexibility and more precise insulin delivery than do multiple daily injections, and thus can reduce the frequency of severe hypoglycemia. However, when CSII was compared to multiple daily injections in randomized crossover or controlled trials in children or adolescents, generally there was no significant difference in HbA1c. This review briefly summarizes the current state of knowledge regarding the use of CSII in pediatric and adolescent patients with type 1 diabetes mellitus.

Introduction
The goals of intensive management of diabetes have been clearly established by the Diabetes Control and Complications Trial (DCCT) [1]. The two main goals in the management of diabetes are: (1) the avoidance of sustained hyperglycemia to prevent the well-documented long-term micro- and macrovascular complications and (2) the avoidance of recurrent episodes of hypoglycemia, which, especially in the younger years, may adversely affect cognitive function as well as cause emotional morbidity for both child and parents. The never-ceasing challenge faced by diabetics and their caregivers has through the years inspired continuing efforts to find ways and means for achieving better control of blood glucose levels. These include the development of insulin pumps, attempting to mimic the complex mechanism of insulin secretion. The first such pumps, available since the late 1970s [2], proved to be problematic and initial enthusiasm soon waned. With the development of smaller, more efficient and user-friendly pumps, continuous subcutaneous insulin infusion (CSII) is rapidly gaining in popularity and in its present form would appear to be the most physiological method of insulin delivery available.

The following is a brief summary of the current state of knowledge regarding CSII, including its advantages and disadvantages, as used in pediatric patients with type
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1 diabetes mellitus (T1DM). Most of the data were discussed in the pediatric consensus document that has been published recently [3].

Data Sources

All articles found in MEDLINE from 1996 to April 2007 that contained the words ‘CSII’ or ‘insulin pump therapy’ in children and/or adolescents were included. There were 159 articles listed, including 39 review articles and one consensus statement.

The Basics of CSII

The pump consists of a device holding a syringe filled with insulin that is delivered by a controlled mechanism pushing the plunger of the syringe down to infuse insulin into the subject via an infusion set inserted into the subcutaneous tissue. It is an open-loop system able to simulate the pattern of insulin secretion with a continuous 24-hour ‘basal’ delivery of insulin upon which are superimposed mealtime ‘boluses’. The basal rate is set to the minimum insulin needed to suppress gluconeogenesis and ketogenesis while keeping blood glucose levels within the normal range without inducing hypoglycemia. The mealtime boluses are calculated with the use of an algorithm and depend on the caloric and nutritive composition of the meal (an option that is not used by all), the capillary glucose concentration before the meal and the anticipated level of physical activity after the meal. The basal and bolus functions of the pump permit separate determination and adjustment of both these insulin requirements as well as flexibility in timing, amounts of nutritional intake and physical activity, allowing for wide variations in lifestyle (fig. 1).

Notable features available in different pumps include: small incremental changes (0.025 or 0.05 unit) in basal rates, important when the total daily insulin dose is low (infants and toddlers); automatic calculation of correction boluses based on insulin-to-carbohydrate ratios and insulin sensitivity factors; direct communication with a blood glucose meter, which can assist with bolus dose calculation; alarm features that can remind a child if a meal bolus is missed, and a pump memory able to review insulin boluses, carbohydrate intake used in bolus calculations and blood glucose levels, which can be most useful in the counseling of patients regarding their diabetes management.

Patient Selection

According to the consensus statement on the use of CSII in the young ages [3], and according to our experience, all pediatric patients with T1DM are potential candidates for the insulin pump, without any age limit. Thus CSII can be safely initiated at diagnosis [4] or anytime thereafter [5]; however prior experience with the use of

Fig. 1. a MDI of short- and long-acting insulin analogs. MDI allow flexibility of insulin administration (aspart) with meals and a relatively constant level of insulin for basal needs without meals (glargine). However, it does not resolve the necessary changes of insulin dosage with the ‘dawn’ and ‘dusk’ phenomena and physical activity. b Insulin pump therapy (CSII). The basal rate supplies a continuous flow of insulin. The basal rate is increased in the early morning and the afternoon hours when the ‘dawn’ and ‘dusk’ phenomena occur. The basal rate can be adjusted to physical activity and even be temporarily stopped. The insulin pump allows flexibility.
insulin syringes and pens might be of importance in case of pump malfunction and, therefore, we usually educate our patients on their use first before switching to CSII. CSII should be strongly considered (1) for children with recurrent severe hypoglycemia [6, 7], unacceptable fluctuations in blood glucose levels regardless of HbA1c [8], suboptimal diabetes control [6], a tendency to develop ketosis, microvascular complications and/or risk factors for macrovascular complications [9] and with good metabolic control but an insulin regimen that unacceptably compromises lifestyle, (2) for competitive athletes, (3) for children with needle phobia, and (4) for young children, especially infants [5, 10–13].

**Current Experience with CSII Therapy in Children and Adolescents**

Pump therapy should be initiated only after a decision has been made jointly by the child, parent(s) and diabetes team. The consensus report [3] further advises that a pediatric multidisciplinary diabetes team experienced in insulin pump therapy is required to initiate and maintain children successfully on CSII, with frequent contact between the family/child and diabetes team after pump initiation.

Knowledge of pump functions as well as management skills, including proper infusion set insertion, are essential. Weinzierl et al. [10] have found that in young children CSII initiation must include an assessment of caregivers to ensure proper supervision, including responsibility for pump management and blood glucose monitoring.

CSII may be discontinued temporarily or permanently in children or adolescents wishing to return to injection therapy, or when there are conditions putting the child at risk, e.g., recurrent diabetic ketoacidosis (DKA) due to pump mismanagement, ineffective pump management or intentional insulin overdosing to cause hypoglycemia [3].

**Type of Insulin Used in CSII**

Many children show rapid fluctuations of their blood glucose levels, a situation demanding rapid adjustment of the insulin dose. Used in CSII, rapid-acting insulin analogs were found to result in a modest but significant reduction in HbA1c as compared with soluble (regular) insulin [14]. Rapid-acting insulin analogs also allow insulin to be delivered during or after the meal, and more frequent bolus doses can be given to correct abnormal blood glucose levels. Although no controlled studies in children are available, the consensus report [3] recommends the use of rapid-acting insulin analogs for CSII [3]. However, in our experience, ‘ketone-prone’ patients or patients with a tendency to catheter occlusion during the night may benefit from the addition of basal insulin such as insulin glargine injection to decrease the risk of DKA. We have a few patients on this mode of therapy with good compliance and with significant reduction in DKA episodes.

**Calculation of Total Daily Insulin Requirements**

The basis for calculating the insulin requirement at the time of pump treatment initiation depends upon the insulin requirement while on multiple daily injections (MDI) and the level of glycemic control. In children with good glycemic control and a low frequency of hypoglycemia, the total dose may need to be reduced by 10–20% [11, 15], and with frequent hypoglycemia, the dose should be reduced by 20%. The basal rate is set to the minimum insulin needed to suppress gluconeogenesis and ketogenesis while keeping blood glucose levels within the normal range without inducing hypoglycemia. Typically 30–50% of the total daily dose is required for basal needs [16] and this is programmed in hourly intervals according to the circadian variation of the patient’s insulin sensitivity, which is age dependent [17]. In adolescents, decreased insulin sensitivity is seen particularly in the early morning (dawn phenomenon) and to a lesser extent in the late afternoon (dusk phenomenon). This leads to a typical two-waved basal rate profile. The PedPump Study Group [18] noted that younger children often need more basal insulin between 21.00 and 24.00 h.

Carbohydrate counting is a prerequisite for successful basal-bolus therapy. The premeal boluses are dependent on meal carbohydrate intake, circadian variation of insulin sensitivity, current blood glucose levels and planned activity. Various algorithms exist that assist in calculating insulin-to-carbohydrate ratios. In the Pedpump Study Group report [18], more than seven daily boluses were associated with significantly better HbA1c values [18]. In very young children or fussy eaters, some parents prefer to administer the bolus after the meal [19] in order to adjust it to the actual food intake. However, missed boluses are associated with poor glycemic control [20].

The quantity of the corrective insulin bolus depends upon insulin sensitivity and is calculated as the difference between the current blood glucose level and the target level. Some pump models offer calculation tools for this purpose, others require manual formula calculation.
Advantages of CSII

Glycemic Control
With CSII, insulin administration is more precise and better matched to food intake and there is less variability of insulin absorption. A number of trials demonstrated a decrease in glucose excursion with CSII with continuous monitoring by glucose sensors [8, 22–26]. The long-term target, however, remains achievement of a near-normal HbA1c, which expresses the control attained over a period of months and serves as a surrogate marker for the degree of risk of late complications. Recently, there has been an increased awareness of the impact of glucose variability on overall blood glucose control and the risk for diabetes-related complications, which may be increased in those with greater glucose excursions.

Numerous studies involving several cohorts with a total of more than 900 pediatric patients on CSII [6, 7, 10–12, 15, 21–23, 27–41] reported a significant improvement in metabolic control, with a decrease of 0.5–1% in HbA1c. However, when CSII was compared to MDI in randomized crossover trials in children [42] or adolescents [43] and in randomized controlled trials of short duration in diabetic toddlers and young children [5, 13], there was no significant difference in HbA1c values. One randomized controlled trial [24] reported a significantly lower HbA1c in pediatric patients receiving CSII when compared to that of patients receiving MDI with glargine. However, in yet another study in pediatric patients, in which CSII was compared with MDI with glargine [44], there were no significant differences in metabolic control or incidence of hypoglycemia or ketoacidosis.

Hypoglycemia
Hypoglycemia is a serious risk associated with intensive therapy. Recurrent episodes of hypoglycemia at a young age have been associated with neurocognitive dysfunction. The fear of hypoglycemia prevalent in adolescents and families of children with T1DM may pose a barrier to improved glycemic control [45, 46]. Several observational pediatric trials [6, 15, 28, 41] found a decrease in the rate of severe hypoglycemic episodes with CSII despite decreasing HbA1c values, but none of the randomized controlled trials [5, 13, 24, 42, 43] have shown a significant difference in the frequency of severe hypoglycemia.

Plasma glucose concentrations are often difficult to manage during prolonged periods of physical activity in patients with T1DM, and there is no way to suspend the action of long-acting insulin analogs once they have been injected subcutaneously. The Diabetes Research in Children Network (DirecNet) [47] demonstrated that the risk of hypoglycemia is sharply increased both during and on the night following a period of aerobic exercise of moderate intensity in pediatric patients maintained on a fixed basal insulin replacement regimen. However, the risk of hypoglycemia was markedly reduced in patients with an insulin pump by suspending the basal insulin infusion during exercise [48]. Another study [49] compared prolonged exercise in patients with CSII who either received half of the regular basal rate (temporary basal) during exercise or underwent temporary interruption of insulin delivery; the rate of hypoglycemia during exercise was similar in both groups, but a trend towards an increased rate of late hypoglycemia was observed in the temporary basal group [49].

Overall it would appear that CSII allows for greater flexibility in physical activity and may safely decrease the risk of hypoglycemia, particularly when the pump is suspended during prolonged activity.

Quality of Life
The improvement in lifestyle may be the most important reason for choosing CSII by the patient or parents. Evidence indicates that with CSII quality of life (QOL) and patient satisfaction are at least equal to or greater than with MDI [5, 21, 50, 51]. Parents of infants and children reported that switching from injections to CSII granted them greater freedom and flexibility in their lives [52, 53]. Adolescents also expressed a high level of satisfaction with pump therapy, noting that the increased flexibility in diet and the daily schedule gave a greater sense of control and independence, with fewer physical complaints [37].

Disadvantages of CSII
As CSII has grown in popularity, patients and physicians have begun to recognize some of its limitations.
Risk of Hypoglycemia

Pump therapy has the potential for hypoglycemia resulting from inappropriate insulin administration, whether intentional or unintentional [54]. With the current generation of pumps, a pump memory provides information on the insulin administered and a safety lock-out feature acts to prevent hypoglycemia.

Risk of DKA

The lack of a subcutaneous depot of intermediate- or long-acting insulin and the short half-life of serum insulin during CSII increase patient susceptibility to ketonemia and DKA secondary to dislodgment or occlusion of the infusion set or pump failure [54]. Interruption of insulin may be intentional, to allow patients to participate in certain activities, or unintentional, caused by catheter occlusion, battery failure or depleted insulin supply. As with injection therapy, however, DKA can be prevented by adhering to published DKA prevention guidelines [55]. Since the alarm devices now available do not warn against leakage or dislodgment, it is recommended [3] that blood glucose should be monitored frequently and consistently with parental supervision; when the levels are elevated and/or when feeling ill, urine or serum ketones should also be tested to permit rapid appropriate intervention to avoid DKA.

Infusion Site Reactions

A few studies have recorded the incidence of skin irritation, lipohypertrophy, scarring and infusion site infections in children. The efforts to minimize these risks should include the strict adherence to proper infusion site preparation, insertion and rotation.

Weight Gain

Concerns have been raised that the improved glycemic control and greater flexibility in eating achieved with CSII might contribute to a greater weight gain than with other therapies. This, however, has not been borne out by a number of pediatric studies, which found no excess weight gain with CSII [30, 42, 54].

Psychosocial Stress

The adoption of more intensive diabetes management coupled with the constant reliance on a medical appliance can weigh heavily on the patient and the family. The metabolic and psychosocial impacts of CSII therapy were examined in a meta-analysis that included five pediatric studies [56]. This did not reveal any consistent differences in anxiety, depression, QOL, self-esteem or family functioning [56].

Cost of CSII

In most countries the cost of a pump and related supplies is higher than the cost of MDI therapy. The additional costs for personnel involved in the initial education and training of patients and their caregivers as well as subsequent support of pump users should also be taken into account.

In summary, on the strength of these reports and studies, the verdict has generally been in favor of the use of insulin pump therapy in children and adolescents, its

### Table 1. Randomized and observational trials comparing MDI with CSII

<table>
<thead>
<tr>
<th>Authors (year of publication)</th>
<th>Number of patients</th>
<th>Mean age (range) years</th>
<th>Mean HbA1c with MDI, %</th>
<th>Mean HbA1c with CSII, %</th>
<th>Mean duration of CSII months</th>
<th>Number of severe hypoglycemic episodes with MDI</th>
<th>Number of severe hypoglycemic episodes with CSII</th>
<th>Number of DKA episodes with CSII</th>
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</thead>
<tbody>
<tr>
<td><strong>Randomized trials</strong></td>
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<tr>
<td>Fox et al. (2005) [5]</td>
<td>26</td>
<td>3.8 (1–6)</td>
<td>7.46</td>
<td>7.24</td>
<td>6</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Wilson et al. (2005) [13]</td>
<td>19</td>
<td>3.6 (1.7–6.1)</td>
<td>8.04</td>
<td>7.8</td>
<td>12</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Doyle et al. (2004) [24]</td>
<td>32</td>
<td>12.5 (8–21)</td>
<td>8.1</td>
<td>7.2</td>
<td>4</td>
<td>4</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Weintrob et al. (2003) [42]</td>
<td>23</td>
<td>11.8 (9.4–13.9)</td>
<td>8.1</td>
<td>8</td>
<td>3.5</td>
<td>3</td>
<td>1</td>
<td>0</td>
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<tr>
<td>Cohen et al. (2003) [43]</td>
<td>16</td>
<td>14.2 (14.5–17.9)</td>
<td>8.57</td>
<td>8.15</td>
<td>6</td>
<td>4</td>
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<td>1</td>
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<td><strong>Observational trials</strong></td>
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<tr>
<td>Weinzimer et al. (2004) [10]</td>
<td>65</td>
<td>4.5 (1.4–6.9)</td>
<td>7.3</td>
<td>7.1</td>
<td>12</td>
<td>78/100 patient years</td>
<td>37/100 patient years</td>
<td>4</td>
</tr>
<tr>
<td>Shehadeh et al. (2004) [12]</td>
<td>15</td>
<td>3.8 (1–6)</td>
<td>8.2</td>
<td>8.18</td>
<td>12</td>
<td>0.36/patient year</td>
<td>0.29/patient year</td>
<td>0</td>
</tr>
<tr>
<td>Plotnick et al. (2003) [28]</td>
<td>95</td>
<td>12 (4–18)</td>
<td>8.1</td>
<td>7.7</td>
<td>12</td>
<td>not available</td>
<td>not available</td>
<td>1</td>
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<tr>
<td>Nimri et al. (2006) [41]</td>
<td>279</td>
<td>17.7 (1.6–40)</td>
<td>8.5</td>
<td>7.8</td>
<td>29</td>
<td>94.6/100 patient years</td>
<td>34.4/100 patient years</td>
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</table>
definite advantages being considered to outweigh considerably its possible disadvantages. Table 1 summarizes the randomized and observational trials comparing CSII with MDI.

Conclusions

In most pediatric centers a major gap between the target of a near-normal HbA1c, as set by the DCCT [1,9,40], and its actual achievement remains, as evidenced by comprehensive documentation [57]. To press towards this goal every effective therapy should be made available to as many pediatric patients as possible. Accumulating evidence suggests that CSII is not only a feasible, safe and well-accepted mode of therapy for pediatric T1DM patients, but has proven to provide improved glycemic control and QOL, as compared with MDI, without any notably greater risk. Minimizing the risks of CSII entails the same interventions that promote safety in all T1DM patients: proper education, frequent blood glucose monitoring, attention to diet and exercise and the maintenance of communication with the diabetes team [3]. The ‘recipe’ for successful pump treatment must be tailored to each individual patient and in all cases must have the continuing support of the experienced multidisciplinary diabetes team. The recent introduction of a real-time continuous glucose monitoring system providing readings 24 h a day constitutes a tool that will allow clinicians to far better utilize the variable basal rate capability of current insulin pumps. Similarly, analysis of postprandial glycemic excursions can provide a more rational method of dividing daytime insulin replacement between basal and bolus doses in CSII-treated patients. Preliminary results using real-time continuous glucose monitoring in youths with T1DM have been very promising [58].

Granted that no treatment of T1DM will ever be perfect until there is feedback control of insulin delivery (i.e., a closed loop), the recent approval of a sensor-augmented insulin pump (open-loop technology) suggests that we may finally be at the threshold of the development of a practically applicable artificial pancreas.

References


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