Original Article

Basal rates and circadian profiles in continuous subcutaneous insulin infusion (CSII) differ for preschool children, prepubertal children, adolescents and young adults


Objective: Initiation of continuous subcutaneous insulin therapy (CSII) requires an appropriate basal rate profile. Different approaches exist; however, there is a lack of evidence-based recommendations, especially in young children.

Study design: In this large multicenter survey, 5941 CSII patients from the German/Austrian prospective documentation system (DPV) were analyzed. Patients were divided into four age groups: <6 yr (n = 837), 6 to <12 yr (n = 1739), 12 to <18 yr (n = 2985) and 18 to <25 yr (n = 380). Basal insulin requirement and diurnal distribution were evaluated based on the most recent documentation for each patient.

Results: Basal insulin requirement differed significantly between the four age groups (<6: 0.25 ± 0.12; 6 to <12: 0.33 ± 0.12; 12 to <18: 0.43 ± 0.15; 18 to <25: 0.35 ± 0.13 U/kg; p < 0.001). Circadian insulin profiles were markedly different between the younger and older age groups. In addition to age, longer diabetes duration, female gender, higher HbA1c and lower body mass index standard deviation score (BMI-SDS) were related to higher basal insulin requirement per kilogram of body weight.

Conclusions: Age of the patient is the primary factor that influences both total daily requirement and circadian distribution of basal insulin in CSII. Experience from a large database may therefore facilitate the initiation of pump therapy in pediatric patients.

Rainer Bachrana, Peter Beyerb, Christof Klinkertc, Bettina Heidtmannd, Joachim Rosenbauere and Reinhard W Hollf, for the German/Austrian DPV Initiative, the German Pediatric CSII Working Group and the BMBF Competence Network Diabetes

aPediatric Practice, D-46147 Oberhausen, Germany; bProtestant Hospital, Pediatric Clinic, D-46047 Oberhausen, Germany; cPediatric Practice, D-32052 Herford, Germany; dCatholic Children’s Hospital Wilhelmstift, D-22149 Hamburg, Germany; eInstitute for Biometrics and Epidemiology, German Diabetes Center, D-40225 Duesseldorf, Germany; and fDepartment of Epidemiology, University of Ulm, D-89081 Ulm, Germany

Key words: adolescents – basal insulin rate – children – CSII – diabetes mellitus type 1

Corresponding author: Rainer Bachran, MD, Pediatric Practice, Dudelerstr. 9, 46147 Oberhausen, Germany. Tel: +49 208 682077; fax: +49 208 6258123; e-mail: bachran@t-online.de

Submitted 21 February 2011. Accepted for publication 21 March 2011
Introduction

During the past decade, diabetes therapy with continuous subcutaneous insulin infusion (CSII) dramatically increased in pediatric diabetes care, especially among preschool children (1). Several studies indicate better glycemic control, less severe hypoglycemia, and better quality of life with CSII therapy (2–5), whereas treatment costs were in most cases higher compared with multiple daily injection (MDI) therapy (6, 7). While recommendations for basal rate profiles in adolescents and adults have been published before (8, 9), no sound data on larger groups of patients are available in the very young age group.

To initiate CSII therapy, the basal insulin dose needs to be determined. The basal rate usually comprises 30–50% of the total daily insulin dose (6, 10), but different centers use different pathways to identify an adequate basal rate. In the United States, Bode's approach (11) for CSII initiation, which uses three to four different basal rates per d, is common practice. Walsh (12) even promotes to start with a constant basal rate. In Germany, Renner’s circadian basal rate profile derived from experience in adults is frequently used to start CSII in children also (13).

Therefore, at present there is no generally accepted recommendation on how to start CSII in different age groups, and on which additional factors to consider. The aim of our study was to collect objective information from a large group of children on CSII, in order to answer this question and facilitate the initiation of pump therapy.

Methods

Data for this large standardized multicenter survey were taken from the German/Austrian prospective documentation system (DPV) for diabetes care. Between 1995 and March 2008, a total of 40 149 patients with type 1 diabetes, aged between 0 and <25 yr, from 277 diabetes centers were documented. Inconsistent data were reported back to the centers every 6 months for correction (14). Data collection was approved by the institutional review board at Ulm University and is in accordance with the Declaration of Helsinki.

Patients treated with CSII and with complete data (basal rates between 0.05 and 1.0 U/kg) were 5941 and were identified and analyzed. The most recent basal rate from each patient was assumed to represent their respective optimal distribution. According to the German Pediatric Working Group on CSII, recommended basal rates should be based on fasting tests over a period of 6–8 h. Basal rate profiles from patients using regular human insulin were shifted back by 1 h to account for the slower onset and longer duration of action compared with a rapid-acting insulin analog, which was used in 86.5% of all patients.

Patients were divided into four age groups: preschool, <6 yr (n = 837); prepubertal, 6 to <12 yr (n = 1739); adolescent, 12 to <18 yr (n = 2985); and adult, 18 to <25 yr (n = 380). The multiple of the mean (MOM) method was used to adjust HbA1c values to the DCCT normal range (4.05–6.05%). Body mass index (BMI) values were transformed to standard deviation scores (SDSs) using German reference data (15).

Descriptive statistics (mean ± SD or proportions) were calculated. To adjust for confounding determinants of hourly basal insulin requirement, a generalized multiple linear regression model was applied. Least square means using observed marginal frequencies of categorical covariates with adjustment for multiple comparisons according to Tukey-Kramer were used for comparison of groups. A p-value <0.05 was considered as significant. SAS 9.2 was used for all statistical analyses.

Results

Mean age (±SD) of the total study group was 13.2 (±4.8) yr, mean diabetes duration 6.3 (±3.9) yr, 47% were male and 86% of the children used short-acting insulin analogs. Basic characteristics of the four different age groups are presented in Table 1. The mean total daily insulin dose (12.6–52.5 IU), as well as the daily basal insulin (5.1–25.2 IU) increased from the youngest to the oldest age group, whereas the mean total daily insulin per kilogram body weight was highest in the adolescent group. In parallel, the mean basal rate per kilogram of body weight showed substantial differences between the four groups with the highest basal requirement during puberty (Table 1). The percentage of basal insulin related to total insulin was again considerably higher in adolescents.

The circadian distribution of basal insulin differed markedly among the four age groups (Fig. 1). All four groups showed a bimodal diurnal profile with an episode of low basal rate apparently reflecting high insulin sensitivity at lunchtime (11:00–13:00 h). In preschool children, basal insulin requirement was highest between 19:00 and 22:00 h, with a second small peak between 5:00 and 8:00 h. Prepubertal children displayed a high peak between 4:00 and 7:00 h, and a smaller peak between 17:00 and 22:00 h. Both in adolescents and in young adults, we identified the highest insulin requirement between 4:00 and 7:00 h and a smaller peak between 16:00 and 19:00 h.

In a multiple regression analysis with basal dose as dependent variable, increasing age, longer diabetes
duration, and higher HbA1c values were related to higher basal insulin requirement (all p < 0.0001), whereas the use of short-acting insulin analogs (p < 0.001), male gender (p < 0.05), and higher BMI standard deviation score (BMI-SDS) (p < 0.01) were related to lower basal insulin doses. After adjustment for these confounders, the mean basal insulin requirement per kilogram of body weight was 0.41 U/kg in adolescents, compared to 0.30 U/kg in preschool children (p < 0.001).

Discussion

The use of CSII for the treatment of type 1 diabetes patients, especially in young children and adolescents, has remarkably increased over the last years in many countries (1, 16) and guidelines define indication for CSII in pediatric patients of different age groups (17). A large number of clinical studies have established that CSII in pediatrics is safe and effective (1, 7, 18). Most studies indicated that glycemic control was similar or better compared to MDI therapy, while the incidence of severe hypoglycemia was consistently reduced (1–3, 19). Inconsistent data have been reported for the rate of ketoacidosis (2, 20–22). In contrast, reported quality of life in patients and families favors CSII (2, 23), and only a small portion of patients, predominantly adolescents, will switch back to MDI therapy (24). Increasingly CSII is used as first-line therapy at diabetes onset in preschool children (1), and the use of insulin analogs has become standard in CSII (17).

These recent developments require contemporary recommendations for basal insulin delivery after initiation of pump therapy. According to the recommendations of several pediatric societies, the basal rate should be programmed in hourly intervals, according to the patient’s circadian variation in insulin sensitivity (6) and based on individual fasting tests over a period of 6–10 h (9). Several studies clearly demonstrate that circadian variations in insulin requirements are age dependent (9, 25–27).

Several pediatric diabetes centers have developed rules to initiate CSII therapy. According to Phillip, the total daily insulin requirement during MDI is calculated. Depending on glycemic control, this figure may be reduced by 10–20% or more in case of frequent hypoglycemia or high total insulin dose during MDI, then using 30–50% as daily basal rate (6, 28). The

Table 1. Patient characteristics and daily insulin requirement by age group (mean ± SD, percentage)

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (&lt;6 yr)</th>
<th>Group 2 (6 to &lt;12 yr)</th>
<th>Group 3 (12 to &lt;18 yr)</th>
<th>Group 4 (18 to &lt;25 yr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>837</td>
<td>1739</td>
<td>2985</td>
<td>380</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>4.4 ± 1.4</td>
<td>10.2 ± 1.6</td>
<td>15.8 ± 1.7</td>
<td>20.8 ± 2.2</td>
</tr>
<tr>
<td>Boys (%)</td>
<td>51</td>
<td>44</td>
<td>47</td>
<td>46</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>103.4 ± 11.4</td>
<td>136.1 ± 14.1</td>
<td>161.3 ± 12.0</td>
<td>171.0 ± 10.3</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>18.0 ± 4.1</td>
<td>34.1 ± 10.5</td>
<td>56.6 ± 13.9</td>
<td>70.0 ± 13.7</td>
</tr>
<tr>
<td>BMI</td>
<td>16.6 ± 1.4</td>
<td>17.8 ± 2.3</td>
<td>21.2 ± 3.4</td>
<td>23.8 ± 4.0</td>
</tr>
<tr>
<td>BMI-SDS</td>
<td>0.56 ± 0.86</td>
<td>0.38 ± 0.76</td>
<td>0.53 ± 0.85</td>
<td>0.73 ± 1.0</td>
</tr>
<tr>
<td>HbA1c (%) (DCCT)</td>
<td>7.45 ± 1.19</td>
<td>7.39 ± 1.03</td>
<td>8.14 ± 1.42</td>
<td>8.49 ± 1.78</td>
</tr>
<tr>
<td>DM duration (yr)</td>
<td>2.1 ± 1.3</td>
<td>4.7 ± 2.5</td>
<td>7.3 ± 3.7</td>
<td>10.3 ± 4.9</td>
</tr>
<tr>
<td>Total insulin dose per day (IU/d)</td>
<td>12.6 ± 5.12</td>
<td>25.73 ± 11.01</td>
<td>48.14 ± 16.70</td>
<td>52.48 ± 16.68</td>
</tr>
<tr>
<td>Total basal insulin dose per day (IU/d)</td>
<td>5.08 ± 2.61</td>
<td>10.31 ± 5.31</td>
<td>19.78 ± 9.16</td>
<td>25.18 ± 9.75</td>
</tr>
<tr>
<td>Basal insulin (% from total)</td>
<td>40.5</td>
<td>40.1</td>
<td>41.2</td>
<td>48.0</td>
</tr>
<tr>
<td>Total insulin (IU/kg/d)</td>
<td>0.71 ± 0.27</td>
<td>0.74 ± 0.21</td>
<td>0.84 ± 0.23</td>
<td>0.76 ± 0.24</td>
</tr>
<tr>
<td>Basal insulin (IU/kg/d)</td>
<td>0.25 ± 0.12</td>
<td>0.33 ± 0.12</td>
<td>0.43 ± 0.15</td>
<td>0.35 ± 0.13</td>
</tr>
<tr>
<td>Patients on insulin analogs (%)</td>
<td>89.1</td>
<td>85.3</td>
<td>86.9</td>
<td>83.1</td>
</tr>
</tbody>
</table>

BMI, body mass index; BMI-SDS, body mass index standard deviation score; DM, diabetes mellitus.

Fig. 1. Circadian distribution of basal insulin in four age groups (% of daily insulin requirement).
German Pediatric CSII Working Group in children and adolescents makes similar recommendations, including additional tests under fasting conditions to optimize basal and prandial doses. In Germany, the biphasic dawn–dusk basal rate profile reported by Renner in adult CSII patients was historically used in many pediatric centers (13).

In 2004, the German Pediatric CSII Working Group developed sliding ruler scales to recommend initial basal rates for various pediatric age groups based on DPV-Wiss data with initial basal rates based on body weight (9). However, since that time experience in preschool children has increased dramatically and the use of insulin analog has become standard. As insulin resistance improves gradually after puberty, a separate recommendation for the first years after puberty is also desirable, as these patients are often treated by pediatric diabetologists in Germany and Austria. A clear shift is observable from a more pronounced dusk and a lesser dawn phenomenon in the youngest group to a more pronounced dawn and a lesser dusk phenomenon in adolescents and young adults, which may be attributed to shifts of counter-regulating hormones in different age groups (29).

The group of patients included in this large multicenter survey is typical for pediatric patients and displays metabolic control similar to other large, multinational studies (19, 30). Multiple regression analysis identified diabetes duration, gender and BMI as additional determinants of basal insulin requirement – the inclusion of these factors into a prediction model might therefore further improve the recommendations of initial basal rate.

In conclusion, both daily basal insulin requirement and circadian profile are highly age-specific in young diabetic patients. In addition, higher HbA1c, longer diabetes duration, female gender and higher BMI are related to higher basal insulin doses per kilogram of body weight. These facts have to be considered when initiating CSII therapy in pediatric patients, in order to optimize basal rate in CSII faster and easier.

Acknowledgements

We thank all members of the German pediatric working group on CSII for collecting and documenting data in DPV. Data collection and analysis were supported by Roche Diabetes Care AG, Switzerland, Novo Nordisk Germany, and the German Federal Ministry of Education and Research (Diabetes Competence Network, FKZ 01GI0859).

References


