Effect of carbohydrate treatment on mild symptomatic hypoglycaemia, assessed by continuous glucose monitoring

T Larsen, P Banck-Petersen, R Due-Andersen, T Høi-Hansen, U Pedersen-Bjergaard, B Thorsteinsson*

Abstract

Background: Appropriate self-treatment of mild symptomatic hypoglycaemia is essential to prevent severe hypoglycaemia. Danish national guidelines recommend 10–20 g of refined carbohydrate (CH) initially, followed by a non-specified amount of unrefined CH.

Aim: Our aim was to explore the effect of the amount of CH taken on glucose concentrations recorded by the MiniMed Continuous Glucose Monitoring System (CGMS) at mild symptomatic hypoglycaemic episodes.

Method: A total of 125 adult patients with type 1 diabetes underwent 6 days of CGMS. HemoCue blood glucose determinations were used for calibration. All mild symptomatic episodes with a concomitant CGMS value ≤3.5 mmol/l were included in the analysis. Participants completed a detailed diary documenting all meals and snacks, insulin doses, and episodes and self-treatment of hypoglycaemia. CGMS values recorded 30 and 60 minutes after the episode were compared to CH intake. An initial intake of <10 g CH was defined as under treatment, and an intake of >20 g CH as over treatment. Treatment target was CGMS values of 3.6–10.0 mmol/l; values ≤3.5 mmol/l were defined as insufficient treatment, and values >10.0 mmol/l as overshooting the target.

Results: A total of 126 mild symptomatic episodes was experienced in 52 (42%) of the patients. Initial carbohydrate intake could be calculated for 93 episodes. At 30 minutes, under treatment was associated with increased risk of insufficient response (57% versus 30%; $p<0.01$). At 60 minutes, over treatment was associated with increased risk of overshooting the target (23% versus 7%; $p<0.05$). An independent effect of follow-up intake of unrefined CH is not detectable within the first 60 minutes after treatment.

Conclusion: Current guidelines for treatment of mild symptomatic hypoglycaemia are appropriate to ensure achievement of the glycaemic target.

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Key words

Type 1 diabetes; symptomatic hypoglycaemia; treatment; CGMS

Introduction

Risk of hypoglycaemia is a major limitation in achieving optimal glycaemic control in type 1 diabetes.[1] Appropriate intake of carbohydrate (CH) is a cornerstone in the treatment of mild hypoglycaemia with the purpose of relieving symptoms and preventing further development into severe hypoglycaemia. Although guidelines for treatment are available,[2–4] the effect of such treatment has – to the best of our knowledge – not been reported.

Present guidelines are partly arbitrary, partly empirical, and partly based on experimental studies in patients with type 1 diabetes subjected to insulin-induced mild symptomatic hypoglycaemia by use of the glucose clamp technique[5] or intravenous insulin injections.[6] From these experiments it is concluded that the ingestion of 15–20 g of glucose is an effective therapy.[5,6] The recent introduction of continuous glucose monitoring has now made it possible to study – in the daily life of the patient with diabetes – the effect of glucose self-treatment of mild hypoglycaemia.

We assessed the effect of the amount of CH taken at mild symptomatic hypoglycaemic episodes in daily life using subcutaneous glucose monitoring in a cohort of patients with type 1 diabetes. The results were compared to the Danish national guidelines for treatment of mild hypoglycaemia.[4]

Authors

T Larsen, RN, Research Nurse
P Banck-Petersen, RN, Research Nurse
R Due-Andersen, MD, Research Fellow
T Høi-Hansen, MD, PhD, Research Fellow
U Pedersen-Bjergaard, MD, Senior Research Fellow
B Thorsteinsson, MD, DMSc, Chief Physician

Endocrinology Section, Division of Internal Medicine I, Hillerød Hospital, DK-3400 Hillerød, Denmark

***Correspondence to:**
T Larsen, Endocrinology Section, Division of Internal Medicine I, Hillerød Hospital, DK-3400 Hillerød, Denmark
Tel: +45 4829 6403
Fax: +45 4829 4783
e-mail: tolar@fa.dk

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Patients and methods

All 262 patients with type 1 diabetes for longer than two years from a cohort included in a study of hypoglycaemia in 1999[7] were invited to participate in the study in 2002.

A total of 125 patients gave written informed consent to participate (Table 1), while the remaining patients did not participate for various reasons.[8] Type 1 diabetes was defined by insulin therapy from the time of diagnosis and a random C-peptide concentration <300 pmol/l (<600 pmol/l if venous blood glucose concentration >12 mmol/l). The study was approved by the regional medical ethics committee.

The patients underwent six days of continuous subcutaneous glucose monitoring applying a Medtronic MiniMed Continuous Glucose Monitoring System (CGMS).[9] Calibration measurements were performed four times a day by a HemoCue B-glucose Analyzer in order to obtain optimal accuracy of the calibration curve.

A diary was kept by participants during the study period for documentation of all meals and snacks, insulin doses, and episodes of mild hypoglycaemia. Mild hypoglycaemia was defined as episodes with symptoms of hypoglycaemia, familiar to and manageable by the patient, with concomitant CGMS values ≤3.5 mmol/l.

Self-treatment of mild hypoglycaemia with refined CH (sugar) was calculated according to a standard scheme from the Danish Diabetes Association.[10] Predefined categories of answers, for example grams of sugar taken, were deliberately avoided in order not to bias patients' immediate reactions to the episodes.

The calculated intake of refined CH was compared with the recommended intake of 10–20 g of refined CH as stated in the Danish national guidelines.[4] These guidelines also recommend follow-up treatment with unrefined CH (no quantity specified). Initial intake of less than 10 g of refined CH was defined as under treatment and intake of 20 g or more as over treatment.

Females/males (%)	36/64
Age (years)	46±11
Duration of diabetes (years)	22±12
≥4 insulin injections per day (%)	89
HbA_{1c} (%) (normal range 4.1–6.4%)	8.3±1.0

Table 1. Clinical characteristics of the study population (figures are % or mean ±SD where indicated)

The effect of the CH intake at the episode was examined by CGMS values recorded 30 and 60 minutes after the episode. At these times we set the target for adequate response to the treatment to be CGMS values of 3.6–10.0 mmol/l, while values ≤3.5 mmol/l were defined as insufficient response and values >10.0 mmol/l were considered as overshooting the target.

Standard descriptive statistics were used to characterise the study population, and comparisons were made by non-parametric methods (Chi-square test). Data were processed using the SPSS software package (version 11.5). The level of statistical significance was chosen as $p<0.05$ (two-sided).

Results

A total of 126 mild symptomatic episodes with CGMS values ≤3.5mmol/l was recorded by 52 (41%) of the patients. The median nadir CGMS value at the episodes was 2.3 mmol/l. In 93 (74%) of the episodes (in 51 patients) the initial CH intake could be calculated, while the remaining answers concerning CH intake were too imprecise to allow calculation.

Thirty (32%) episodes were initially treated according to guidelines, and follow-up treatments (whether initial treatment had been taken or not) were recorded in 43 (46%) of the episodes. Initially, 35 (38%) of the episodes were over treated, while 28 (30%) were under treated. In total, only 14 (15%) of the episodes were initially treated and followed-up according to guidelines, while 10 (11%) of the episodes were initially under treated with no follow-up.

Initial treatment and follow-up treatment were inversely correlated. Thus, when episodes were initially under treated, follow-up treatment was recorded in 65% of the episodes; when initial treatment was adequate, follow-up treatment was seen in 47% of the episodes; and when episodes were initially over treated, follow-up treatment was indicated in 31% of the episodes ($p<0.05$).

The effects of CH intake as measured by CGMS 30 and 60 minutes after the hypoglycaemic episodes are shown in Tables 2 and 3 respectively.

After 30 minutes, an adequate response (CGMS value 3.6–10.0 mmol/l) was observed in 58 (62%) of the episodes, while 34 (37%) of the episodes had lower values, and one episode had a higher value (Table 2). In 16 (57%) of the episodes that were initially under treated, the 30-minute CGMS value was ≤3.5 mmol/l, compared to 30% and 26% following adequate treatment and over treatment, respectively ($p<0.01$). An effect of follow-up treatment

	CGMS value after 30 min (mmol/l) ≤3.5	3.6–10.0	>10.0	Total
Number of episodes	34	58	1	93
Initial treatment				
• Adequate treatment (10–20 g CH)	9	21	0	30
• Over treatment (>20 g CH)	9	25	1	35
• Under treatment (<10 g CH)	16	12	0	28
Initial treatment ± follow-up				
• Adequate sugar + follow-up	3	11	0	14
• Adequate sugar, no follow-up	6	10	0	16
• Over treatment + follow-up	3	8	0	11
• Over treatment, no follow-up	6	17	1	24
• Under treatment + follow-up	9	9	0	18
• Under treatment, no follow-up	7	3	0	10

Table 2. Continuous glucose monitoring system (CGMS) values 30 min after carbohydrate (CH) intake in 93 episodes of mild symptomatic hypoglycaemia with CGMS values ≤3.5 mmol/l

could not be detected after 30 minutes. Thus, CGMS values ≤3.5 mmol/l were seen in 15 (35%) of the episodes with follow-up treatment (21%, 27% and 50% of episodes that were initially adequately treated, over treated, and under treated, respectively), while episodes with no follow-up treatment had CGMS values ≤3.5 mmol/l after 30 min in 19 (38%) of the episodes (38%, 25% and 70% of episodes that were initially adequately treated, over treated, and under treated, respectively; p=0.75).

After 60 minutes, an adequate response (CGMS value 3.6–10.0 mmol/l) was observed in 63 (68%) of the episodes, while 18 (19%) of the episodes had lower values, and 12 (13%) episodes had higher values (Table 3). The number of episodes with insufficient response was halved from 30 to 60 minutes (p<0.01).

	CGMS value after 60 min (mmol/l) ≤3.5	3.6–10.0	>10.0	Total
Number of episodes	18	63	12	93
Initial treatment				
• Adequate treatment (10–20 g CH)	6	23	1	30
• Over treatment (>20 g CH)	4	23	8	35
• Under treatment (<10 g CH)	8	17	3	28
Initial treatment ± follow-up				
• Adequate sugar + follow-up	2	11	1	14
• Adequate sugar, no follow-up	4	12	0	16
• Over treatment + follow-up	2	9	0	11
• Over treatment, no follow-up	2	14	8	24
• Under treatment + follow-up	3	12	3	18
• Under treatment, no follow-up	5	5	0	10

Table 3. Continuous glucose monitoring system (CGMS) values 60 min after carbohydrate (CH) intake in 93 episodes of mild symptomatic hypoglycaemia with CGMS values ≤3.5 mmol/l

The occurrence of CGMS values ≤3.5 mmol/l at 60 min did neither differ between episodes that were initially adequately treated, over treated or under treated (20%, 11% and 29%, respectively; p=0.43) nor when follow-up treatment had been performed or not (16% and 22%, respectively; p=0.49).

CGMS values >10.0 mmol/l at 60 min occurred more frequently following initial over treatment (23%) than after episodes treated with less than 20 g CH (7%; p<0.05).

Discussion

The present study was conducted in order to evaluate the effect of oral glucose intake on mild symptomatic hypoglycaemia in the daily life of patients with type 1 diabetes. In addition, we studied the effect of initial intake of 10–20 g CH as recommended in Danish national guidelines.[4] These guidelines are similar to those from Diabetes UK,[2] whereas guidelines from the American Diabetes Association recommend 15–20 g glucose.[3]

It has previously been reported that only 40% of patients with type 1 diabetes adhere to the recommendations for treatment of mild symptomatic hypoglycaemia.[11] In the present study, adherence was even lower. Only 15% of the episodes were treated according to guidelines, whereas 11% were under treated. The remaining 74% of the episodes were either initially treated with too little or too much glucose or only by follow-up treatment with unrefined CH. No episodes progressed into severe hypoglycaemia. An inverse relationship was observed

between initial treatment and follow-up treatment. Thus, the less glucose taken initially, the more likely follow-up treatment would be used.

A lower CGMS cut-off level of 3.5 mmol/l was chosen for the evaluation of the effect of glucose ingestion on blood glucose level. This level was chosen because it is the lower fasting limit in normal subjects. Moreover, our definition of mild symptomatic hypoglycaemia includes the presence of a glucose concentration less than 3.6 mmol/l, meaning that the presence of CGMS values below this level indicate that the hypoglycaemic episode had not been treated sufficiently.

Following the recommended initial ingestion of at least 10 g glucose, blood glucose was above 3.5 mmol/l after 30 and 60 minutes in about 72% and 85% of the episodes, respectively, but only in 43% and 71% of the episodes treated with less than 10 g glucose. This finding indicates that less than 10 g glucose is not enough when treating mild hypoglycaemia initially.

An upper CGMS cut-off level of 10.0 mmol/l was arbitrarily chosen as an indicator of overshooting the target. Whereas initial over treatment rarely resulted in glucose values above 10 mmol/l after 30 minutes, they were present in a quarter of the episodes after 60 minutes. However, the clinical significance of this finding is less clear than that related to the lower cut-off level. Thus, to conclude that initial intake of 20 g glucose is too much is premature in view of the small number of episodes.

Although follow-up treatment is also recommended, an independent effect of this treatment modality could be detected neither after 30 minutes nor after 60 minutes. However, we cannot exclude an effect of follow-up treatment beyond the first 60 minutes after the episode.

In conclusion, current guidelines for the treatment of mild symptomatic hypoglycaemia are appropriate to ensure the achievement of the glycaemic target in the vast majority of patients, and to avoid early treatment failure; whereas initial treatment with less than 10 g glucose is insufficient.

Although initial treatment with more than 20 g glucose may lead to overshooting the target in a few patients, more studies are needed to define a clinically significant glucose target for overshooting. An independent effect of follow-up treatment with unrefined CH after initial treatment with refined CH is not detectable within the first 60 minutes after treatment.

Healthcare professionals should carefully instruct patients to comply with current guidelines for treating hypoglycaemia in order to secure rapid and adequate correction of symptomatic hypoglycaemia.

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Conflict of interest statement:

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