Improving Epinephrine Responses in Hypoglycemia Unawareness With Real-Time Continuous Glucose Monitoring in Adolescents With Type 1 Diabetes

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OBJECTIVE — To determine whether real-time continuous glucose monitoring (CGM) with preset alarms at specific glucose levels would prove a useful tool to achieve avoidance of hypoglycemia and improve the counterregulatory response to hypoglycemia in adolescents with type 1 diabetes with hypoglycemia unawareness.

RESEARCH DESIGN AND METHODS — Adolescents with type 1 diabetes with hypoglycemia unawareness underwent hyperinsulinemic hypoglycemic clamp studies at baseline to determine their counterregulatory hormone responses to hypoglycemia. Subjects were then randomized to either standard therapy or real-time CGM for 4 weeks. The clamp study was then repeated.

RESULTS — The epinephrine response during hypoglycemia after the intervention was greater in the CGM group than in the standard therapy group.

CONCLUSIONS — A greater epinephrine response during hypoglycemia suggests that real-time CGM is a useful clinical tool to improve hypoglycemia unawareness in adolescents with type 1 diabetes.

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Hypoglycemia unawareness is defined as the onset of neuroglycopenia before autonomic activation (1). Patients have defective symptomatic and counterregulatory responses, in particular impaired epinephrine response to hypoglycemia. Both defective counterregulatory responses and hypoglycemia unawareness constitute the hypoglycemia-associated autonomic failure associated with recurrent iatrogenic hypoglycemia (2–4).

In adults, it has been demonstrated that as little time as 2 to 3 weeks of avoidance of hypoglycemia reverses hypoglycemia unawareness and improves the attenuated epinephrine component of defective counterregulation in affected patients (5–7). Although strict avoidance of hypoglycemia can restore autonomic symptoms of hypoglycemia and improve counterregulatory responses to hypoglycemia, this is difficult to achieve in practice. Real-time continuous glucose monitoring (CGM) allows patients to view their blood glucose levels almost instantaneously and offers potential to reduce hypoglycemia frequency.

This study was designed to determine whether real-time CGM with preset alarms at specific glucose levels would prove a useful tool to achieve avoidance of hypoglycemia and therefore improve the counterregulatory response to hypoglycemia in adolescents with type 1 diabetes with hypoglycemia unawareness.

RESEARCH DESIGN AND METHODS

— Adolescents with type 1 diabetes aged 12–18 years with hypoglycemia unawareness attending Princess Margaret Hospital diabetes clinics were invited to participate. Hypoglycemia unawareness score was determined by the use of modified Clarke's questionnaire (8). This questionnaire has been shown to accurately identify patients with impaired awareness of hypoglycemia for both clinical and research purposes (9). A score of ≥8 is suggestive of hypoglycemia unawareness. Consent was obtained for all participants.

All subjects underwent a hyperinsulinemic hypoglycemic clamp study at baseline to assess hypoglycemic symptoms and hormonal responses. Subjects were then randomized to either standard therapy (standard group) or to the use of real-time (Medtronic Minimed Paradigm REAL-Time System) CGM (CGM group) for 4 weeks. At the end of the 4-week period, all patients underwent a repeat hypoglycemic clamp study.

Hyperinsulinemic hypoglycemic clamp

During this procedure, the antecubital vein was cannulated for insulin and glucose infusion, and blood was sampled from the contralateral hand vein placed in a box heated to 60°C. Regular insulin (Human Actrapid; Novo Nordisk, Crawley, U.K.) was infused at a constant rate of 80 mU/m^2/min. Target plasma glucose levels were achieved by adjusting the rate of infusion of 20% glucose in water. Plasma glucose concentrations were maintained initially at euglycemia (5–6 mmol/l) over a period of 1 h. Following this, blood glucose was lowered over 30 min to a nadir of 2.8 mmo/l. The blood glucose concentration of 2.8 mmol/l was

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maintained for 40 min for the hypoglycemia phase. Euglycemia was then restored.

For the duration of the clamp procedure, blood glucose was analyzed at the bedside using a glucose oxidase technique (YSI 2300; Yellow Springs Instruments, Yellow Springs, OH). Additional samples of arterialised venous blood were taken to measure plasma insulin, glucagon, epinephrine, norepinephrine, cortisol, and growth hormone concentrations.

Study intervention

Following the first hypoglycemic clamp study, both groups were advised to strictly avoid hypoglycemia with fingerstick testing at least four to six times daily to maintain blood glucose levels between 6 and 10 mmol/l for the 4-week period. In addition, the CGM group wore real-time CGM with subcutaneous sensor with preset low alarms at 6 mmol/l and was advised to institute standard hypoglycemia treatment for blood glucose levels below 6 mmol/l with target blood glucose level of 8 mmol/l.

The CGM group received an an additional 2 h of instructions regarding sensor insertion and usage. Sensors were changed every 3 days.

Outcome measures

The major outcome measure was the epinephrine response to hypoglycemia measured during the hypoglycemia clamp study. Plasma epinephrine levels were measured by ELISA (Diagnostika GMBH, Hamburg, Germany) and samples were analyzed in duplicate. The interassay coefficient of variation at 10 pmol/l and 5,460 pmol/l were 2% and 5.5%, respectively.

RESULTS — Eleven subjects were studied, including five subjects in the standard group (age 15.0 ± 0.8 years, A1C 7.9 ± 0.3% since diagnosis, duration 6.5 ± 1.2 years) and six subjects in the CGM group (age 13.8 ± 0.7 years, A1C 7.7 ± 0.2% since diagnosis, duration 5.2 ± 1.4 years).

At baseline, the epinephrine response to hypoglycemia was blunted, and there was no difference between subjects randomized to standard or CGM groups (percentage change 288 ± 151 vs. 214 ± 72%, standard vs. CGM group, respectively; $P = 0.688$). Following the intervention, there was a greater epinephrine response in the CGM group (percentage change 114 ± 83 vs. 604 ± 234%, standard vs. CGM group, respectively; $P = 0.048$). This represents a greater percentage rise in epinephrine concentrations during hypoglycemia following therapy in the CGM group ($P = 0.375$ vs. 0.031, standard vs. CGM group, respectively) as shown in Fig. 1. Peak adrenaline response during hypoglycemia after the intervention was also greater in the CGM group than in the standard group (1,093 ± 221 vs. 572 ± 162 pmol/l; $P = 0.048$). Subjects in the CGM group reported higher adrenergic symptoms scores after the intervention than the standard group (5.4 ± 0.4 vs. 3.4 ± 0.2; $P < 0.001$).

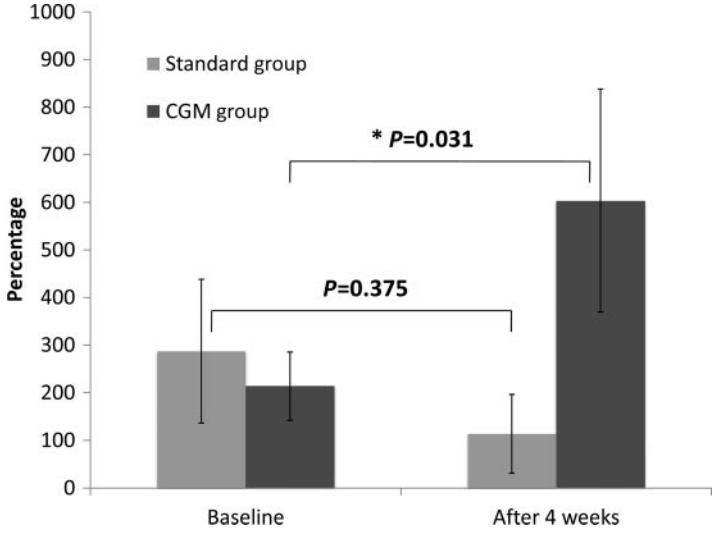

Figure 1—*Change in epinephrine response during hypoglycemia. Data are means ± SE.*

The mean A1C at baseline was 7.9 ± 0.3% for both groups. Following the intervention, there was no deterioration in glycemic control in the standard or CGM group (A1C 7.9 ± 0.4 vs. 8.3 ± 0.3%; $P = 0.587$).

The glucagon response was absent at baseline and after intervention in both groups. There was no change in cortisol and growth hormone responses to hypoglycemia for both groups.

CONCLUSIONS — The epinephrine response to hypoglycemia in patients with type 1 diabetes with hypoglycemia unawareness was greater after the use of real-time CGM with low glucose alarms than with standard medical therapy alone. The use of CGM was not associated with deterioration in A1C. This greater epinephrine response during hypoglycemia suggests that real-time CGM is a useful clinical tool to improve hypoglycemia unawareness in adolescents with type 1 diabetes. The high risk of associated severe hypoglycemia requires that hypoglycemia unawareness be recognized and treated.

This study demonstrates that blunted counterregulatory responses to hypoglycemia do occur in adolescents with a relatively short duration of diabetes. In addition to the blunted epinephrine response, most of these subjects reported no adrenergic symptoms during their baseline hypoglycemic clamp study.

A limitation of this study is the sample size. However, evaluating counterregulatory response with hypoglycemia clamp studies is a robust method, and this technique limits inclusion of a large number of subjects.

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T.T.L. wrote the manuscript and collected and researched data. J.H. reviewed and edited the manuscript, collected data, and contributed to the study design. R.J.D. reviewed and edited the manuscript and contributed to the study design. E.M.L. reviewed and edited the manuscript and researched data. E.A.D. contributed to discussion, researched data, and reviewed and edited the manuscript. T.W.J. contributed to the study design, researched data, and wrote the manuscript.

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