FreeStyle Navigator Continuous Glucose Monitoring System Use in Children With Type 1 Diabetes Using Glargine-Based Multiple Daily Dose Regimens

Results of a pilot trial Diabetes Research in Children Network (DirecNet) Study Group

STUART WEINZIMER, MD[1]
DONGYUAN XING, MPH[2]
MICHAEL TANSEY, MD[3]
ROSANNA FIALLO-SCHARER, MD[4]
NELLY MAURAS, MD[5]
TIM WYSOCKI, PHD[6]
ROY BECK, MD, PHD[2]
WILLIAM TAMBORLANE, MD[7]
KATRINA RUEDY, MSPH[2]
THE DIABETES RESEARCH IN CHILDREN NETWORK (DIRECNET) STUDY GROUP*

In a previous pilot study of the FreeStyle Navigator Continuous Glucose Monitoring System, hereafter referred to as "Navigator," in 30 children and adolescents with type 1 diabetes using insulin pumps, we found that Navigator use averaged >130 h per week over 13 weeks and mean A1C level dropped from 7.1 ± 0.6 to 6.8 ± 0.7% ($P = 0.02$) (1). The current study evaluated whether the Navigator was similarly tolerated over 13 weeks in 27 children aged 4–17 years with type 1 diabetes using glargine-based, multiple daily injection(MDI) insulin regimens. Subjects averaged >100 h/week of Navigator use. Mean A1C level fell from 7.9 ± 1.0% at baseline to 7.3 ± 0.9% at 13 weeks ($P = 0.004$). High satisfaction with the Navigator was reported on the Continuous Glucose Monitor Satisfaction Scale. These encouraging pilot study results support the inclusion of MDI users in longer-term randomized clinical trials of continuous glucose monitors.

RESEARCH DESIGN AND METHODS — Institutional review boards at each of the Diabetes Research in Children Network (DirecNet) centers approved the study protocol and consent/assent forms. Research methods were virtually identical to those employed in our previous Navigator (Abbott Diabetes Care; Alameda, CA) study (1) except that all subjects were treated with glargine-based MDI treatment. Other eligibility requirements were as follows: subjects must *1*) be aged 3–17 years, *2*) have type 1 diabetes for a duration ≥1 year, *3*) have access to a home computer equipped with E-mail, and *4*) have a parent/older subject who comprehended English. Subjects were excluded for asthma, cystic fibrosis, psychiatric disorder, and use of glucocorticoids. Subjects were selected for participation from the existing patient population at each center.

There was a 1-week run-in period during which Navigator use was blinded to collect baseline glucose data, followed by unblinded home use for 3 months. To blind subjects to the results from the Navigator sensor readings, Abbott Diabetes Care provided software that modified the display on the receiver so that the sensor readings would not display but results of FreeStyle glucose testing would be displayed. During this run-in period, subjects were required to perform at least four glucose tests daily. Because of difficulty using the sensor or other problems, 5 of 32 subjects withdrew during the run-in phase. The remaining 27 subjects were asked to use the Navigator continuously and were instructed on how to use the sensor data to make management decisions (2). Subjects downloaded the Navigator weekly and transmitted the data to the clinical and coordinating centers. Patients were seen at 3, 7, and 13 weeks and were called at 0.5, 2, 4, 8, and 10 weeks to review glucose data and adjust treatment. A1C was measured with the DCA 2000+ (Bayer). Parents and subjects ≥9 years of age completed the PedsQL Diabetes Module (3), Fear of Hypoglycemia Survey (4,5), and the Continuous Glucose Monitor Satisfaction Scale (6).

Glycemic indexes were calculated giving equal weight to each of the 24 h of the day. SD, mean amplitude of glycemic excursions (7), and mean absolute rate of change (8) were calculated. Paired *t* tests were used to compare baseline with 9- to 13-week data.

RESULTS — The mean ± SD age of the 27 subjects was 11.0 ± 3.9 years (range 4–17), median (quartiles) duration of diabetes was 3.4 (2.0, 5.2) years, and mean A1C was 7.9 ± 1.0%. A1C was ≤7.5% in 10 subjects and >7.5% in 17 subjects. Four subjects dropped out before the 13-week visit, and the remaining

From the [1]Department of Pediatrics, Yale University School of Medicine, New Haven, Connecticut; the [2]Jaeb Center for Health Research, Tampa, Florida; [3]University of Iowa Health Care, Iowa City, Iowa; the [4]University of Colorado Health Sciences Center, Denver, Colorado; [5]Nemours Children's Clinic, Jacksonville, Florida; the [6]Division of Psychology and Psychiatry, Nemours Children's Clinic, Jacksonville, Florida; and the [7]Department of Pediatric Endocrinology, Yale University School of Medicine, New Haven, Connecticut.

Address correspondence and reprint requests to Stuart Weinzimer, MD, c/o DirecNet Coordinating Center, Jaeb Center for Health Research, 15310 Amberly Dr., Suite 350, Tampa, FL 33647. E-mail: direcnet@jaeb.org.

Received for publication 15 October 2007 and accepted in revised form 12 December 2007.

Published ahead of print at http://care.diabetesjournals.org on 20 December 2007. DOI: 10.2337/dc07-1995.

*A full list of the members of the Diabetes Research in Children Network (DirecNet) Study Group can be found in the APPENDIX.

Abbreviations: MDI, multiple daily injection.

Table 1—*Major outcomes summary*

	Baseline	Weeks 1–4	Weeks 5–8	Weeks 9–13	*P*#	*P***
n	27	27	25*	23*		23
Navigator use per week (h)						
Wear	153 ± 30	107 ± 52	114 ± 50	107 ± 44		0.25
Glucose readings	99 ± 42	79 ± 42	79 ± 41	77 ± 41		0.12
Meter tests per day	4.9 ± 1.4	3.2 ± 1.7	2.9 ± 1.7	2.6 ± 1.6		0.16
n	27		24	23	23	
A1C (%)						
All subjects	7.9 ± 1.0		7.4 ± 0.8	7.3 ± 0.9	0.004	
Baseline <7.5	7.0 ± 0.5		6.7 ± 0.6	6.6 ± 0.5	0.03	
Baseline >7.5	8.5 ± 0.7		7.8 ± 0.6	7.8 ± 0.7	0.02	
n	26†	26†	23†	23	22‡	23‡
Mean glucose (mg/dl)						
All subjects	191 ± 34	172 ± 18	171 ± 23	181 ± 31	0.25	0.05
Baseline <7.5	170 ± 28	162 ± 21	161 ± 23	159 ± 22	0.38	0.98
Baseline >7.5	205 ± 31	179 ± 13	177 ± 22	196 ± 29	0.49	0.03
% Values 71–180 mg/dl						
All subjects	46	55	55	50	0.32	0.04
Baseline ≤7.5	56	62	61	62	0.36	0.54
Baseline >7.5	40	51	52	42	0.68	0.06
Hypoglycemia (% values mg/dl)						
≤70	4.4	3.3	4.0	3.4	0.36	0.75
≤60	2.6	1.6	1.9	1.6	0.27	0.63
≤50	1.39	0.76	0.93	0.79	0.30	0.52
≤40	0.85	0.40	0.57	0.42	0.33	0.36
Hypoglycemia area§	0.75	0.43	0.54	0.44	0.25	0.60
Hyperglycemia (mg/dl)						
Percent >180	50	42	41	47	0.54	0.07
Percent >200	42	33	32	38	0.45	0.06
Percent >250	25	14	15	19	0.12	0.01
Percent >300	11.2	4.5	5.0	7.3	0.07	0.008
Hyperglycemia area‖	40	25	26	32	0.17	0.02
Glucose lability						
SD (mg/dl)	74	67	67	69	0.12	0.04
MAGE (mg/dl)	147	128	126	127	0.001	0.66
Mean absolute rate of change¶	0.84	0.81	0.77	0.79	0.16	0.44

Data are means ± SD or % unless otherwise indicated. *Three subjects dropped prior to 7-week visit, and another dropped prior to 13-week visit; one subject had baseline A1C ≤7.5%, and three subjects had baseline A1C >7.5%. †Subjects with <24 h of Navigator glucose readings were excluded from calculation of glycemic indices. ‡Number of subjects with at least 24 h of Navigator glucose readings for both time points. §Total area <70 mg/dl; reflects both percentage and severity of glucose values in the hypoglycemic range. ‖Total area above 180 mg/dl; reflects both percentage and severity of glucose values in the hyperglycemic range. ¶Rate of change calculated using consecutive Navigator readings 10 min apart (milligrams per deciliter per min). #Baseline vs. weeks 9–13. **Weeks 1–4 vs. weeks 9–13. MAGE, mean amplitude of glycemic excursions.

23 completed the 13-week study. As shown in Table 1 (Table 1), subjects averaged 100 h of sensor wear per week, and the frequency of sensor use did not change significantly after the run-in phase. A similar trend was observed in meter measurements.

Mean A1C fell from 7.9 ± 1.0% at baseline to 7.3 ± 0.9% at 13 weeks (P = 0.004), with the greatest reduction being when baseline A1C level was >7.5%. Mean glucose concentration dropped early (baseline vs. weeks 1–4, P = 0.002), but no further drop occurred during weeks 9–13. There was a similar trend for the percentage of glucose values in the target range of 71–180 mg/dl (P = 0.004). Glycemic variation decreased (baseline vs. weeks 9–13, P = 0.001 for mean amplitude of glycemic excursions), and there were no severe hypoglycemia events during the study. There was no association between number of meter tests per day and A1C.

Subjects and parents reported high overall satisfaction with the Navigator on the Continuous Glucose Monitor Satisfaction Scale, with average item scores of 3.5 ± 0.5 for subjects and 3.8 ± 0.4 for parents on a 5-point Likert scale in which 3.0 is a neutral score. Fear of Hypoglycemia Survey and PedsQL scores did not change, although on the Continuous Glucose Monitor Satisfaction Scale at 13 weeks subjects and parents both agreed that the sensor "makes me feel safer knowing that I will be warned about low blood glucose before it happens" (mean 3.9 and 4.5 for subjects and parents, respectively).

CONCLUSIONS — In this pilot study, we assessed whether continuous glucose monitoring could be utilized con-

sistently and effectively in youth with type 1 diabetes on glargine-based MDI therapy. We found that the majority of subjects used the Navigator on an almost daily basis, parents and patients were very satisfied with the device, and indexes of glycemic control improved. Additionally, all 23 subjects who completed the 13-week visit elected to continue using the Navigator during an optional continuation phase. Improvements in glycemic control were seen shortly after initiation of continuous glucose monitoring and were sustained for the duration of the study.

The Navigator provided a safe and effective complement to standard glucose meter monitoring, even though none of the subjects in this study had used insulin pump therapy and none had prior experience with the use of an external transcutaneous device. Although these subjects were not strictly comparable with pump patients in our prior Navigator study (e.g., baseline A1C levels were higher in the MDI subjects), major outcomes were similar in these MDI-treated patients. Moreover, the findings from both of the DirecNet Navigator pilot studies are in marked contrast to the results of our study of the GlucoWatch (9), a device that children and adolescents with type 1 diabetes found too difficult to use consistently.

While our results are encouraging, they must be viewed cautiously because there was no concurrent control group and follow-up only lasted 3 months. Nevertheless, these preliminary data support the inclusion of MDI patients in longer-term randomized clinical trials evaluating the effectiveness of continuous glucose monitor use in children with type 1 diabetes.

Acknowledgments— This research was supported by the following National Institutes of Health/National Institute of Child Health & Development Grants HD041919-01, HD041915-01, HD041890, HD041918-01, HD041908-01, and HD041906-01. Clinical centers also received funding through the following General Clinical Research Center grants: M01 RR00069, RR00059, RR 06022, and RR00070-41. Abbott Diabetes Care, Alameda, CA, provided the FreeStyle Navigator Continuous Glucose Monitoring Systems and the FreeStyle Blood Glucose Meter test strips.

APPENDIX

TheDiabetes Research in Children Network (DirecNet) study group, by clinical center listed in alphabetical order.

Personnel are listed as principal investigator (PI), co-investigator (I), and coordinators (C): *1*) Barbara Davis Center for Childhood Diabetes, University of Colorado, Denver, CO: H. Peter Chase, MD (PI); Rosanna Fiallo-Scharer, MD (I); Laurel Messer, RN (C); Barbara Tallant, RN, MA (C); and Victoria Gage, RN (C). *2*) Department of Pediatrics, University of Iowa Carver College of Medicine, Iowa City, IA: Eva Tsalikian, MD (PI); Michael J. Tansey, MD (I); Linda F. Larson, RN (C); Julie Coffey, MSN (C); and Joanne Cabbage (C). *3*) Nemours Children's Clinic, Jacksonville, FL: Tim Wysocki, PHD, ABPP (PI); Nelly Mauras, MD (I); Larry A. Fox, MD (I); Keisha Bird, MSN (C); and Kim Englert, RN (C). *4*) Division of Pediatric Endocrinology and Diabetes, Stanford University, Stanford, CA: Bruce A. Buckingham, MD (PI); Darrell M. Wilson, MD (I); Paula Clinton, RD, CDE (C); and Kimberly Caswell, APRN. *5*) Department of Pediatrics, Yale University School of Medicine, New Haven, CT: Stuart A. Weinzimer, MD (PI); William V. Tamborlane, MD (I); Elizabeth A. Doyle, MSN (C); Heather Mokotoff, MSN (C); Amy Steffen (C); and Brett Ives, ARNP (C). *6*) Coordinating Center: Jaeb Center for Health Research, Tampa, FL: Roy W. Beck, MD, PHD; Katrina J. Ruedy, MSPH; Craig Kollman, PHD; Dongyuan Xing, MPH; Cynthia R. Stockdale; and Judy Jackson. *7*) University of Minnesota Central Laboratory: Michael W. Steffes, MD, PHD; Jean M. Bucksa, CLS; Maren L. Nowicki, CLS; Carol A. Van Hale, CLS; and Vicky Makky, CLS. *8*) National Institutes of Health: Gilman D. Grave, MD; Mary Horlick, PHD; Karen Teff, PHD; and Karen K. Winer, MD. *9*) Data and Safety Monitoring Board: Dorothy M. Becker, MBBCh; Patricia Cleary, MS; Christopher M. Ryan, PhD; Neil H. White, MD, CDE; and Perrin C. White, MD.

References

1. Diabetes Research in Children Network (DirecNet) Study Group, Buckingham B, Beck RW, Tamborlane WV, Xing D, Kollman C, Fiallo-Scharer R, Mauras N, Ruedy KJ, Tansey M, Weinzimer SA, Wysocki T: Continuous glucose monitoring in children with ype 1 diabetes. *J Pediatr* 151:388–393, 2007
2. Diabetes Research in Children Network (DirecNet) Study Group, Buckingham B, Xing D, Weinzimer S, Fiallo-Scharer R, Kollman C, Mauros N, Tsalikian E, Tamborlane W, Wysocki T, Ruedy K, Beck RW: Use of the DirecNet Applied Treatment Algorithm (DATA) for diabetes management with a real-time continuous glucose monitor (the Freestyle Navigator). *Pediatr Diabetes* 8:1–6, 2007
3. Varni JW, Burwinkle TM, Jacobs JR, Gottschalk M, Kaufman F, Jones KL: The PedsQL™ in type 1 and type 2 diabetes: reliability and validity of the Pediatric Quality of Life Inventory™ Generic Core Scales and Type 1 Diabetes Module. *Diabetes Care* 26:631–637, 2003
4. Clarke WL, Gonder-Frederick LA, Snyder AL, Cox DJ: Maternal fear of hypoglycemia in their children with insulin-dependent diabetes mellitus. *J Pediatr Endocrinol Metab* 11 (Suppl. 1):189–194, 1998
5. Green LB, Wysocki T, Reineck BM: Fear of hypoglycemia in children and adolescents with diabetes. *J Pediatr Psychol* 15: 633–641, 1990
6. The Diabetes Research in Children Network (DirecNet) Study Group: Youth and parent satisfaction with clinical use of the Glucowatch G2 Biographer in the management of pediatric type 1 diabetes. *Diabetes Care* 28:1929–1935, 2005
7. Service FJ, Molnar GD, Rosevear JW, Ackerman E, Gatewood LC, Taylor WF: Mean amplitude of glycemic excursions, a measure of diabetic instability. *Diabetes* 19:644–655, 1970
8. Kovatchev BP, Clarke WL, Breton M, Brayman K, McCall A: Quantifying temporal glucose variability in diabetes via continuous glucose monitoring: mathematical methods and clinical application. *Diabetes Technol Ther* 7:849–862, 2005
9. The Diabetes Research in Children Network (DirecNet) Study Group: A randomized multicenter trial comparing the GlucoWatch Biographer with standard glucose monitoring in children with type 1 diabetes. *Diabetes Care* 28:1101–1106, 2005