Reducing Rates of Severe Hypoglycemia in a Population-Based Cohort of Children and Adolescents With Type 1 Diabetes Over the Decade 2000–2009

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OBJECTIVE—To examine rates of severe hypoglycemia (SH) in a large population-based cohort of children with type 1 diabetes and relationships to HbA1c.

RESEARCH DESIGN AND METHODS—Data from 1,683 children (mean [SD] age at diagnosis 10.5 [4.2]; range 1–18 years) from 2000 to 2009 were analyzed from the Western Australian Children’s Diabetes Database. Rates of SH were related to HbA1c using negative binomial regression.

RESULTS—A total of 7,378 patient-years of data and 780 SH events were recorded. The rate of SH per 100 patient-years peaked at 17.3 in 2001 and then declined from 2004 to a nadir of 5.8 in 2006. HbA1c <7% was not associated with higher risk of SH (incidence rate ratio 1.2 [95% CI 0.9–1.6], P = 0.29) compared with HbA1c of 8–9%.

CONCLUSIONS—In a sample of youth with type 1 diabetes, there has been a decrease in rates of SH and a weaker relationship with glycemic control than previously observed.

Diabetes Care 34:2379–2380, 2011

The threat of hypoglycemia as a consequence of insulin treatment is a major barrier to optimizing glycemic control in type 1 diabetes (1). Previous studies have demonstrated a close relationship between glycemic control and increased rates of severe hypoglycemia (SH) (2). In the 1990s, increased emphasis on strict glycemic control was paralleled with an increase in the rate of SH, particularly in younger children (<6 years) (3,4). Therapies have changed, however, and the objectives in this study were to examine contemporary rates of SH in a large population-based cohort of pediatric type 1 diabetes and changes over the past decade and to investigate relationships with glycemic control.

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Received 19 April 2011 and accepted 17 August 2011.

DOI: 10.2337/dc11-0748

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Statistical analysis

Annual SH incidence rates were calculated by obtaining the total number of SH events and dividing by the total length of follow-up represented by each clinical visit recorded in that year. Initial analyses involved revisiting previously identified risk factors by applying negative binomial regression methodology, as already described (3), to the new data. This was the basis of defining the final models for effect size estimates and age by treatment interaction analysis (6). Analyses were performed using R 2.11.1 and Stata 10 software (StatCorp 2007, Stata Statistical Software: Release 10; StataCorp LP, College Station, TX).

RESULTS—The study included 1,683 children (51% boys). In total, 7,378 patient-years of data were available for analysis, and 780 SH events occurred during the decade. Of all patients, 77.4% had no episodes, 11.8% had one event, 5.2% had two events, and 5.6% had three

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Diabetes Care, volume 34, November 2011
or more episodes. The incidence rate for SH (Fig. 1), adjusted for age and sex, decreased by an average of 14% per year compared with previous year for the first 7 years ($z = 5.33, P < 0.001$) and did not change after that time ($P = 0.446$).

Univariate analysis quantified the annual rate of decline in the SH incidence rate over the decade as 12.1% (95% CI 8.7–15.4, $P < 0.001$) per year.

The mean HbA1c level for the decade was 8.3% (SD 1.5%), with only minor fluctuations. After adjusting for age and sex, the overall trend showed a decline in mean HbA1c levels of 0.07% per year (95% CI 0.009–0.15; $P = 0.03$). Multivariate analysis, adjusting for age and treatment type, showed an HbA1c <7% was not significantly associated with higher risk of SH (incidence rate ratio 1.2 [0.9–1.6]; $P = 0.29$) compared with the reference group of HbA1c 8–9%, which was the average level in our cohort across the decade.

There was no relationship between age and risk of SH and no sex difference. Children with duration of diabetes $>1$ year had a significantly higher risk (incidence rate ratio 3.7 [95% CI 2.4–5.7]; $P < 0.001$ for 1–5 years, increasing thereafter), than those with duration of diabetes $<1$ year. In adolescents ($>13$ years), pump therapy was associated with a reduced incidence of SH (64% lower, $P = 0.048$).

**CONCLUSIONS**—The primary objective of this study was to determine incidence rates of SH in a population-based sample of pediatric type 1 diabetes during a period when there were changes to treatment regimens. This is one of the largest population-based cohorts for which clinical data have been collected prospectively, and this report follows on from rates previously reported for 1992–2002 (3) and 1992–1995 (4). The reduction in the hypoglycemia rate may have resulted from changes in clinical practice (e.g., new insulin regimens, more intensive glucose monitoring, improved management guidelines), but this remains speculative.

Despite the decrease in SH rates, glycemic control has remained relatively static since the middle of the decade. This is similar to a recent report from the Hvidoere group demonstrating no recent improvement in glycemic control (7,8). An important finding was that compared with past studies, the relationship between glycemic control and the risk of SH is now weaker, with no significant increased risk of SH associated with improved glycemic control range from 8–9% to <7%. Another change has been the reduced risk of SH in children aged <6 years (3). This is an important observation in view of concerns regarding the potential effect of hypoglycemia on the developing brain (9).

In summary, in a population-based sample of pediatric type 1 diabetes, rates of SH have decreased during the past decade, and the previously close relationship between tight glycemic control and risk of severe events is now weaker. Although the data are encouraging and suggest that the risk of SH is in part being reduced with modern therapy, the risk remains significant and fear of hypoglycemia continues to be a barrier to optimal glycemic control.

**Acknowledgments**—S.O’C. received a fellowship grant from Novo Nordisk Ltd. in 2010. No other potential conflicts of interest relevant to this article were reported.

S.O’C. collected and researched data and wrote the manuscript. M.N.C. performed statistical analysis, generated the figures, and reviewed and edited the manuscript. M.K.B. provided methodologic, data, and statistical support based on previous publications. E.A.D. contributed to study design, data collection, analysis, and discussion. T.W.J. contributed to study design, data collection and analysis, and reviewed and edited the manuscript.

The authors thank Nirubasini Paramalingam, Telethon Institute for Child Health Research, The University of Western Australia, for assistance with data extraction.

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