

Continuous Glucose Monitoring and the Reality of Metabolic Control in Preschool Children With Type 1 Diabetes

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OBJECTIVE — To determine using the MiniMed continuous glucose monitoring system (CGMS) 1) whether twice-daily insulin injection therapy achieves adequate control in preschool children with type 1 diabetes and 2) whether the CGMS is more informative than self-monitoring of blood glucose (SMBG) regarding glucose control and well tolerated by preschool children and their families.

RESEARCH DESIGN AND METHODS — Ten children <6 years of age with type 1 diabetes were monitored twice using the CGMS. The distribution of glucose values was analyzed, particularly the frequency, duration, and distribution of hypoglycemia. We analyzed the accuracy of the CGMS in detecting hypoglycemia as well as the clinical relevance of the difference between CGMS and SMBG values.

RESULTS — Although hypoglycemia was more frequent during the night (0.8 nighttime episodes \cdot subject⁻¹ \cdot 24 h⁻¹ vs. 0.3 daytime episodes \cdot subject⁻¹ \cdot 24 h⁻¹), the difference did not reach statistical significance ($P = 0.07$). However, nighttime episodes lasted longer than daytime episodes (1.2 vs. 0.2 h \cdot subject⁻¹ \cdot 24 h⁻¹, $P = 0.006$). Hypoglycemia accounted for 7% and normoglycemia for 24%, while hyperglycemia occurred 64% of the time, with postprandial hyperglycemia being an almost universal feature ($94 \pm 7\%$ of all postmeal values). The CGMS correlated well with SMBG without significant clinical discrepancy. The CGMS sensitivity to detect hypoglycemia was 70% with a specificity of 99%; however, the CGMS detected twice as many total episodes as SMBG (82 vs. 40).

CONCLUSIONS — Twice-daily insulin injection rarely achieves control in preschool children with type 1 diabetes. The CGMS is well tolerated by patients and has the advantage of revealing daily glucose trends missed by SMBG.

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The results of the Diabetes Control and Complications Trial (DCCT) emphasized the importance of tight control in reducing microvascular complications of type 1 diabetes. However, tight control tripled the risk of hypoglycemia (1). The inability to replace insulin physiologically or make appropriate fine

changes to insulin dosing results in frequent over- and underinsulinization, leading to swings in blood glucose concentrations. This is more pronounced in preschool children with type 1 diabetes who suffer more frequently from hypoglycemic seizures. They have higher insulin sensitivity due to enhanced peripheral

glucose uptake (2) as well as an unpredictable day-to-day variability in physical activity and eating habits (3).

Conversely, hypoglycemia, particularly at night, is a frequent occurrence in subjects with type 1 diabetes (4). Impaired counter regulatory response even at diagnosis increases the risk (5), often limiting attempts at better control (6). Acute hypoglycemia leads to a transient impairment in cognitive functioning that often endures even after euglycemia is restored (7). Therefore, early detection and treatment of hypoglycemia are crucial. Although long-term consequences of recurrent severe hypoglycemia with seizures are still not clear, most studies associate it with some degree of brain dysfunction, particularly in children <6 years of age at diagnosis (8,9).

Self-monitoring of blood glucose (SMBG) provides an accurate picture of glycemic control at the time the glucose concentration is measured but has the potential to miss daily hypo- and hyperglycemic excursions (10). More frequent measurement with SMBG is often not readily accepted by parents and patients (11), particularly in preschool children, because of the discomfort and struggle to carry out the monitoring.

The continuous glucose monitoring system (CGMS) from Medtronic MiniMed (Northridge, CA) measures interstitial glucose concentration. Interstitial glucose concentrations correlate well with plasma glucose values (12–14). CGMS has been shown to detect hypoglycemia, guide insulin therapy, and improve control in children, adolescents, and adults (15, 16,17). However, other investigators found significant discrepancies between the readings generated by the CGMS and those by SMBG (18,19). Little is known about glycemic control in preschool children. Because of their vulnerability to hypoglycemia and seizures, we carried out the following study to obtain a more precise picture of daily glucose trends in this age-group.

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Abbreviations: CGMS, continuous glucose monitoring system; SMBG, self-monitoring of blood glucose.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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RESEARCH DESIGN AND METHODS

After obtaining institutional review board approval for the protocol and parental consent, 10 children <6 years of age with type 1 diabetes for >6 months and followed at The Texas Children's Hospital Diabetes Care Center were recruited. Subjects were on a twice-daily injection regimen consisting of mixed NPH as the intermediate-acting insulin and lispro (Eli Lilly, Indianapolis, IN) as the rapid-acting insulin. No insulin was administered with lunch; however, two subjects were using an additional morning dose of glargine insulin (Aventis Pharmaceuticals, Bridgewater, NJ) given separately. Subjects were excluded if they were on continuous subcutaneous insulin infusion therapy or medications that alter glucose metabolism.

Before study entry the parents and/or caregivers underwent a review of SMBG, insulin adjustment, and carbohydrate counting. Every subject underwent two 72-h periods of monitoring 1 month apart using the CGMS. HbA_{1c} was measured during each monitoring visit using the Bayer (Tarrytown, NY) DCA 2000 instrument with a nondiabetic range of 4.3–6.3%. The DCA 2000 is certified by the National Glycohemoglobin Standardization Program with HbA_{1c} results comparable with those reported in the DCCT, where relationships to mean blood glucose and risk for vascular complications have been established. Insulin management was done based on the values obtained from self-monitoring, reflecting the standard practice of our clinic.

The CGMS consists of a glucose oxidase-based sensor inserted subcutaneously in an abdominal site and attached via a cable to a monitor that can be worn much like an insulin pump. The chemical reaction creates a current measurable by the device that in turn generates a corresponding glucose value. The monitor takes a reading every 10 s and displays an average every 5 min for a total of 288 readings per day. CGMS is calibrated by entering SMBG readings four times per day. The device allows patients to record their meals and insulin doses. After completion of the monitoring period the device is downloaded and analyzed. In the present study the analysis was done using CGMS Solutions 3.0b software. Parents and investigators were blinded to the results until the child had completed the entire study.

The CGMS was inserted in each child by a certified diabetes educator study nurse at Texas Children's Diabetes Care Center. Parents and/or caregivers were instructed to document at least four daily meter blood glucose measurements for calibration. All subjects used the FreeStyle glucometer (TheraSense, Alameda, CA) for SMBG. Caregivers were instructed not to use alternate sites for testing. They also kept records of mealtime and insulin doses.

Statistical analysis

The data from the CGMS were downloaded and analyzed to identify the number of hypoglycemic episodes and their duration and distribution (daytime versus nighttime). Hypoglycemia was defined as a CGMS or a SMBG glucose value <60 mg/dl. Hyperglycemia was defined as a glucose value >150 mg/dl. We used 80–150 mg/dl as an acceptable range for adequate control because achieving a target glucose range of 80–120 mg/dl is difficult in this very young age-group. Comparison was made between the two sets of data generated by the CGMS and SMBG.

Analysis to evaluate the agreement between the CGMS and SMBG was done using the following criteria defined by Medtronic MiniMed (20). For optimal accuracy, MiniMed recommends a minimal correlation of 0.79 between the two sets of data with a mean absolute error <28%. The company cautions the user to employ clinical judgment in interpreting any result that does not satisfy the above criteria.

To evaluate the ability of the CGMS to correctly detect hypoglycemic episodes, we assigned one of four categories to each paired CGMS measurement with hypoglycemia (blood glucose <60 mg/dl) set as the positive event: 1) true positive (TP) when both CGMS and meter report a value <60 mg/dl; 2) false-positive (FP) when the CGMS reports a value <60 mg/dl, while the meter reports a value >60 mg/dl; 3) true negative (TN) when both modalities report a value >60 mg/dl; or 4) false negative (FN) when the CGMS reports a value >60 mg/dl when the meter reads <60 mg/dl. Sensitivity [TP/(TP + FN)], specificity [TN/(TN + FP)], positive predictive value [TP/(TP + FP)], and negative predictive value [TN/(TN + FN)] were calculated.

We also analyzed the data using the Clarke error grid (21). This method eval-

uates whether the difference between glucose values obtained through two different methods is clinically relevant. For example, a difference of 30 mg/dl between two methods is more relevant when the blood glucose is 50 mg/dl versus when it is 300 mg/dl. The analysis is done as follows. The two sets of values generated by the CGMS and SMBG are plotted against each other. Then the graph is divided into five zones. Zone A includes values that differ by no more than 20% or are in the hypoglycemic range (<70 mg/dl) for both methods. Zone B includes values that differ by >20% but do not lead to significantly different treatment decisions. Zone C includes values that would lead to overcorrection of acceptable blood glucose. Zone D represents values that lead to failure to respond to hypo- or hyperglycemia. Zone E includes dangerous treatment decisions, i.e., giving insulin when the patient is hypoglycemic or vice versa. Each zone is further subdivided into an upper and a lower zone. Clinically acceptable correlation between two methods occurs when >95% of the values fall within zones A and B.

Results are expressed as means \pm SD. Due to the extreme variability in the frequency of hypoglycemic episodes, these particular results were expressed as median (range). The analysis was carried out using Wilcoxon's rank test to compare the 6-month average HbA_{1c} before study entry to the HbA_{1c} at study entry as well as the number and duration of nighttime versus daytime hypoglycemic episodes. Statistical significance was defined as $P < 0.05$. The analysis was carried out using SPSS software version 12.0 (Chicago, IL).

RESULTS— Our study group consisted of 10 patients (8 females and 2 males) with type 1 diabetes. The average age at study entry was 3.65 ± 1.34 years (range 1.75–5.67 years) with disease duration of 1.88 ± 1.38 years (1.00–4.08 years). The average HbA_{1c} at study entry was $8.1 \pm 0.8\%$. There was no difference between the HbA_{1c} (8.6 ± 0.8 vs. $8.5 \pm 0.6\%$, $P = 0.62$), insulin dose (0.7 ± 0.1 vs. 0.7 ± 0.2 units \cdot kg⁻¹ \cdot day⁻¹, $P = 0.57$), or BMI (16.4 ± 1.6 vs. 16.1 ± 1.3 kg/m², $P = 0.14$) recorded during the first and second monitoring episodes.

A total of 22 sensors were inserted; one patient was excluded from the study after his first sensing episode due to fail-

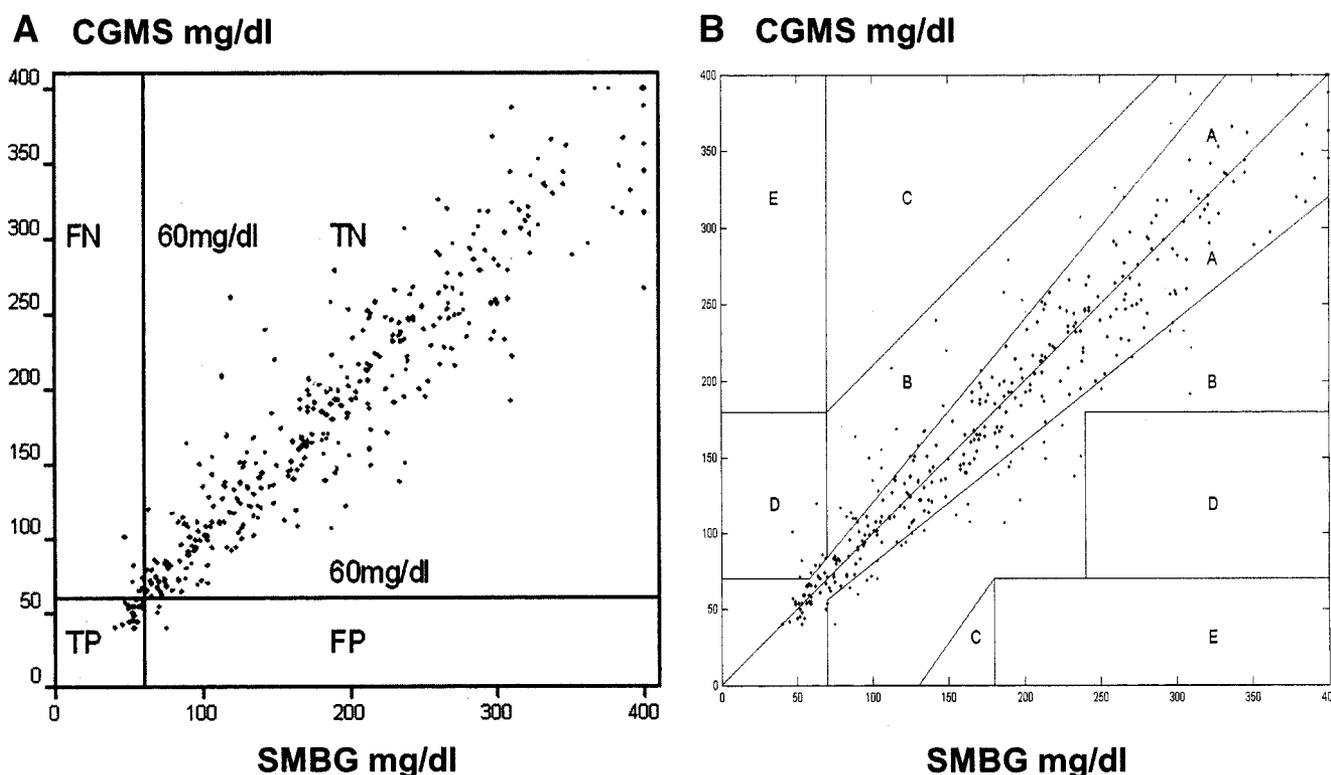


Figure 1—A: Accuracy analysis. The 379 pairs of glucose values were plotted against each other with the meter on the x-axis and CGMS on the y-axis. The graph was divided into four areas by a line crossing the value of 60 mg/dl on each axis. The areas were labeled as true positive (TP), true negative (TN), false-positive (FP), and false negative (FN), respectively, depending on where the point fell on the graph. The number of true positive was 26, true negative 339, false-positive 3, and false negative 11. B: Clarke error grid analysis. A total of 379 paired values were plotted using the Clarke error grid. Of the values, 97.4% fell within the clinically acceptable A and B regions ($n = 369$), 81.3% fell in zone A, and 16.1% in zone B. Only one measurement fell in the upper C region (0.3%) and nine in the upper D region (2.3%).

ure to comply with the study protocol. Three monitoring periods were repeated due to several episodes of disconnection between the sensor and the cable, making the total fraction of nonsatisfactory periods 14%. The total number of monitoring periods analyzed was thus 19, with a median duration of 70 h (range 49–90 h). The total number of CGMS readings was 15,102, with 379 paired CGMS/SMBG readings. The average number of measurements was 7 ± 1 per subject per day. The overall tolerance to the device was excellent, with no reported local irritation or infection. The device did not interfere with the care of the child and was well accepted by all children and families.

We found good agreement between the two methods using Medtronic criteria. The mean correlation coefficient was 0.94 ± 0.04 . The mean absolute error for all monitoring episodes was $12.4 \pm 5.1\%$. Accuracy analysis revealed that the sensitivity of the CGMS to detect hypoglycemia was 70% and the specificity 99%. The positive predictive value of a hypoglycemic

reading obtained via CGMS was 90%, while the negative predictive value was 97% (Fig. 1A). There was good agreement between the two methods as evaluated by the Clarke error grid, with 97.4% of the values falling in the A and B regions (Fig. 1B).

Incidence of hypoglycemia

The total number of hypoglycemic episodes was 82, with a median number of 3 episodes per subject per monitoring period (0–12). We also analyzed the night-day distribution of hypoglycemia. Nighttime was defined as the period from 2200 to 0700, a period during which most preschool children are expected to be asleep (Table 1).

We found that 51% of the hypoglycemic episodes ($n = 42$) out of the total of 82 detected by the CGMS did not have a concomitant finger-stick value. Assuming that the CGMS did not detect all of the hypoglycemic episodes and mislabeled some normal values as hypoglycemia and by using the accuracy data generated

above, we calculated an estimate of the number of true episodes as being 97 rather than 82. The number of episodes that both CGMS and SMBG would detect or the true positives would be 64. Even with this reduced number, the average number of episodes is $1.1 \text{ episode} \cdot \text{subject}^{-1} \cdot 24 \text{ h}^{-1}$. Because the median duration of an episode was 1 h, each subject would still have a total of 60 min of hypoglycemia per 24 h.

There was no difference in the mean CGMS (198 ± 38 vs. 200 ± 45 mg/dl, $P = 0.8$) or SMBG (181 ± 27 vs. 187 ± 38 mg/dl, $P = 0.6$) glucose values between the first and second monitoring episodes. We looked for a possible effect that the CGMS itself might have on glycemic control. However, when we compared the first and second monitoring periods, we found no difference between the total duration of hypoglycemia (median 4.7 vs. 4.2 h/monitoring period, $P = 0.4$) or number of episodes (median 3 vs. 3 episodes/monitoring period, $P = 0.6$). The correlation between the average

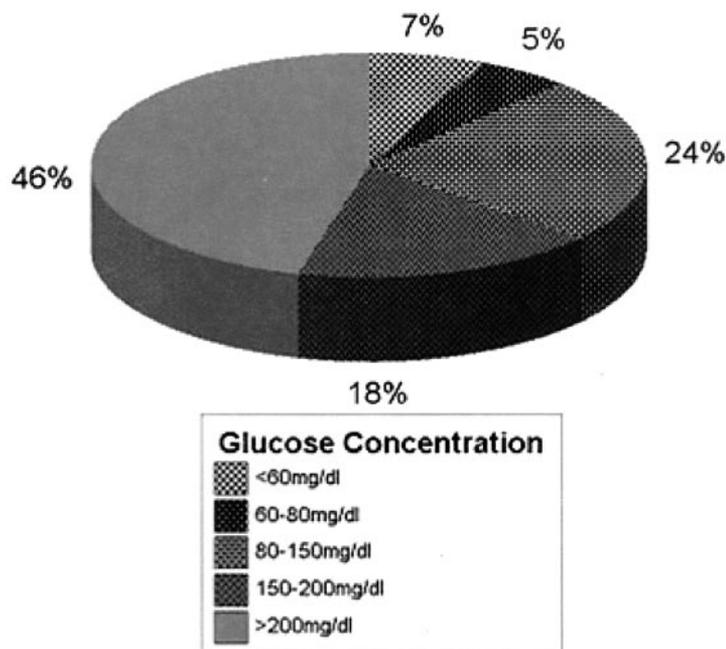


Figure 2—Pie chart depicting the glycemic trends obtained from the CGMS during a 24-h period. Each portion corresponds to a glucose range. The legend below the figure depicts the different ranges. The proportion of the time spent within any given range is expressed as a percentage and shown next to each portion.

HbA_{1c} and the average glucose value recorded by the CGMS for each subject was 0.93 ($P < 0.0001$). However, we found no correlation between either HbA_{1c} or average glucose on one hand and the number or duration of either hypo- or hyperglycemic episodes on the other hand. This was true whether looking at nighttime, daytime, or overall results.

The median number of hyperglycemic episodes was 3 episodes \cdot subject⁻¹ \cdot 24 h⁻¹ (2–4). We found that subjects spent 7% (range 0–22%) of a 24-h period with a glucose value <60 mg/dl, 64% (35–83%) with a glucose value >150 mg/dl, and only 24% (10–49%) of their time with acceptable values (80–150 mg/dl) (Fig. 2).

Furthermore, 72% of all the glucose values exceeding 150 mg/dl were >200 mg/dl, and 55% of the glucose values below 100 mg/dl were <60 mg/dl. We also found that of the 136 documented meals times, $94 \pm 7\%$ of them had a glucose value >200 mg/dl in the 2-h period following the meal. This was distributed as breakfast (93%), lunch (98%), and dinner (92%).

CONCLUSIONS— Glucose monitoring remains the cornerstone of evaluating the efficacy of therapy in subjects

with diabetes (22). Even if faithfully done, SMBG is a snapshot of the real picture with potential to miss fluctuations. With this in mind, we designed our study to assess other means of evaluating current therapeutic regimens in preschool children.

There are several limitations to our study, including the number of subjects. Larger studies of preschool children are needed to confirm our results. Although lacking a control group with normal patients wearing the device, we performed accuracy analysis to detect the rate of false-positives and false negatives. We did not obtain venous blood glucose to com-

pare SMBG and CGMS readings to a laboratory reference method for the following reasons. 1) Obtaining frequent venous samples is difficult to do at home and generally requires a hospital admission. We felt that the hospital stay would not be a true reflection of what really happens at home, particularly for this very young age-group. 2) The FreeStyle meter used in our study has a very good correlation with venous samples, with 96.7% of the values falling within a 10% difference of laboratory reference methods (23).

In a study of children on continuous subcutaneous insulin therapy, Boland et al. (10) reported similar results with frequent hypoglycemic events and significant postprandial hyperglycemia; however, their study subjects were older children and adolescents (mean age 11.6 ± 4.6 years). They reported the same number of hypoglycemic episodes (0.9 vs. 1.0 episodes \cdot subject⁻¹ \cdot day⁻¹) but a higher duration of nighttime hypoglycemia (117 vs. 72 min \cdot subject⁻¹ \cdot night⁻¹) than in our study. This is somewhat surprising, as we would have expected our younger subjects on twice-daily injections to have longer and more frequent hypoglycemic episodes than older children on continuous subcutaneous insulin infusion. We found a good correlation between the CGMS and SMBG when MiniMed criteria were used. However, correlation is expected to be good in any two methods measuring the same entity (i.e., glucose); we therefore used the Clarke error grid to test the clinical relevance of the difference when present. The grid revealed differences in 2.6% of the time. Almost all children had several hypoglycemic episodes during each of the 72-h periods. The CGMS had a low sensitivity and mislabeled 30% of hypoglycemic

Table 1—The 24-h distribution of hypoglycemic episodes

Hypoglycemic episodes	Median per subject	Range
Total duration of monitoring (h)	70.0	49–90.5
Total number of episodes per 24 h (h)	1.1	0–4
Number of nighttime episodes per 24 h	0.8	0–2
Number of daytime episodes per 24 h	0.3	0–2
Total duration of episodes per 24 h (h)	1.4	0–5.3
Duration of night time episodes (h)	1.2	0–5.3
Duration of daytime episodes (h)	0.2	0–1.3

Summary of the number, duration, and night/day distribution of hypoglycemic episodes recorded by the CGMS.

mic episodes as normal values; however, only 18% of those mislabeled episodes had CGMS values >80 mg/dl. We did not find a difference between the frequencies of nighttime versus daytime hypoglycemia, although nighttime episodes lasted longer. This is likely due to the fact that nighttime episodes are frequently undetected. We also found that most children spend significant portions of their time with unacceptable glucose values (either hypo- or hyperglycemia). Adequate control was achieved only 24% of the time. Even after correction by using the accuracy data, each subject still had a median of 1 h of hypoglycemia in a 24-h period.

Our results show that twice-daily subcutaneous insulin injection in preschool children with type 1 diabetes fails to achieve glycemic control. In fact, treatment often overshoots, with a high risk of hypoglycemia (55%) when glucose concentrations fall to <100 mg/dl, or under-shoots, with hyperglycemia (>200 mg/dl) occurring 72% of the time when concentrations reach 150 mg/dl. Hyperglycemia is another dominant feature of glucose control in this age-group. In fact, 64% of their time was spent with a glucose value >150 mg/dl, and postprandial hyperglycemia was almost a universal feature (94%). This is a surprising fact because all of our subjects were on lispro insulin.

In conclusion, our study shows that preschool children with type 1 diabetes have suboptimal control on twice-daily insulin injection therapy, with frequent and prolonged hypoglycemia, especially at night, lasting up to 1 h per day. The CGMS reveals trends in blood glucose that current means of evaluating the adequacy of therapy (including HbA_{1c} and SMBG) are not able to discern. We also conclude that the HbA_{1c} is not an ideal indicator of adequate control in this age-group but merely reflects an average of extreme highs and lows. In light of the frequency of postprandial hyperglycemia, it might be beneficial to measure postmeal glucose values in this age-group. Further studies are needed to investigate whether basing clinical decision making on the CGMS results in better control in preschool children. Given the serious complications associated with hyperglycemia and neurological risks of hypoglycemia, especially in younger patients, failure of current therapeutic regimens using twice-daily insulin injections to achieve reason-

able control is an area for concern. It is necessary to study newer types of insulin or insulin pump therapy in preschool children with type 1 diabetes in order to reduce daily glycemic excursions.

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