Mini-Dose Glucagon Rescue for Hypoglycemia in Children With Type 1 Diabetes

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OBJECTIVE — Children with type 1 diabetes are frequently difficult to manage during times of gastroenteritis or poor oral intake of carbohydrates because of mild or impending hypoglycemia. The present study describes the effective use of small doses of subcutaneous glucagon in these children.

RESEARCH DESIGN AND METHODS — We analyzed 33 episodes of impending or mild hypoglycemia in 28 children (ages 6.6 ± 0.7 years). All were healthy except for type 1 diabetes and an episode of gastroenteritis. Using a standard U-100 insulin syringe, children ages ≤2 years received two "units" (20 μg) of glucagon subcutaneously and those ages >2 years received one unit/year of age up to 15 units (150 μg). If the blood glucose did not increase within 30 min, the initial dosage was doubled and given at that time. We used patients' self-glucose monitoring devices, aqueous glucagon, standard insulin syringes, and frequent phone contact with a physician and/or a diabetes nurse educator in this study.

RESULTS — Blood glucose was 3.44 ± 0.15 mmol/l before and 8.11 ± 0.72 mmol/l 30 min after glucagon. In 14 children, relative hypoglycemia recurred, requiring retreatment (3.48 ± 0.18 to 6.94 ± 0.72 mmol/l). In four children, a third dose was required. The glucagon was well tolerated. In 28 of the 33 episodes of impending hypoglycemia, the children remained at home and fully recovered. Five children were taken to their local hospital because of concerns of dehydration or fever, but none for hypoglycemia.

CONCLUSIONS — Mini-dose glucagon rescue, using subcutaneous injections, is effective in managing children with type 1 diabetes during episodes of impending hypoglycemia due to gastroenteritis or poor oral intake of carbohydrate.

Diabetes Care 24:643–645, 2001

When a child or adolescent with type 1 diabetes is unable to consume or absorb oral carbohydrate because of nausea and vomiting associated with gastroenteritis or because of oppositional behavior in a young child, hypoglycemia should be anticipated. To maintain blood glucose concentrations in a safe range, parents either seek medical attention in their local emergency room or must force oral carbohydrate in an ill child, which frequently leads to more vomiting.

Based on previous clinical experience (1), a treatment algorithm was developed. We hypothesized that the use of small, subcutaneous doses of aqueous glucagon and home glucose monitoring would prevent or treat mild hypoglycemia in diabetic children with gastroenteritis without increasing the frequency of vomiting.

RESEARCH DESIGN AND METHODS

Study protocol

Standard self-monitoring techniques for blood glucose were used. When our diabetes treatment staff identified a child with gastroenteritis or oppositional behavior with a relatively low blood glucose concentration (<4.44 mmol/l), placing the child at risk for hypoglycemia, a baseline blood glucose was measured. The parents were then instructed to dilute their glucagon (1 mg/ml) according to the pharmaceutical instructions included in the standard emergency glucagon kit (Eli Lily, Indianapolis, IN). The glucagon dose was drawn in a standard U-100 insulin syringe. The child received a subcutaneous dose of glucagon on the basis of his/her age: two "units" (20 μg) on the insulin syringe for children ages ≤2 years and one unit per each year of age in children ages 2–15 years (150 μg). Patients ages > 15 years received only 15 units. The parents were instructed to monitor the glucose at 30-min intervals over the first hour and then at hourly intervals or at shorter intervals, if appropriate, if the child continued to have glucose values <5.5 mmol/l or if the child was not retaining orally administered carbohydrates. Subsequent monitoring was predicated on the initial response to glucagon and the glucose value after 60 min. The parents were in intermittent contact with a diabetes nurse or the physician on call until the clinical problem resolved or the patient was referred to an emergency ward. If at 30 min the glucose was essentially unchanged, the initial dosage was doubled and injected at that time. Once the glucagon was reconstituted, the parents were requested to keep it refrigerated, discard it after 24 h, and replenish their supply immediately after this acute episode. In all cases, at least 500 μg of glucagon was held in reserve (or the family had a second unopened glucagon kit at home).

Patient population

The patients were self-selected by parents calling for assistance. The data were collected over an 18-month period. Two children had two episodes separated by ~10 months each and one child had three

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Received for publication 2 August 2000 and accepted in revised form 27 December 2000.

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

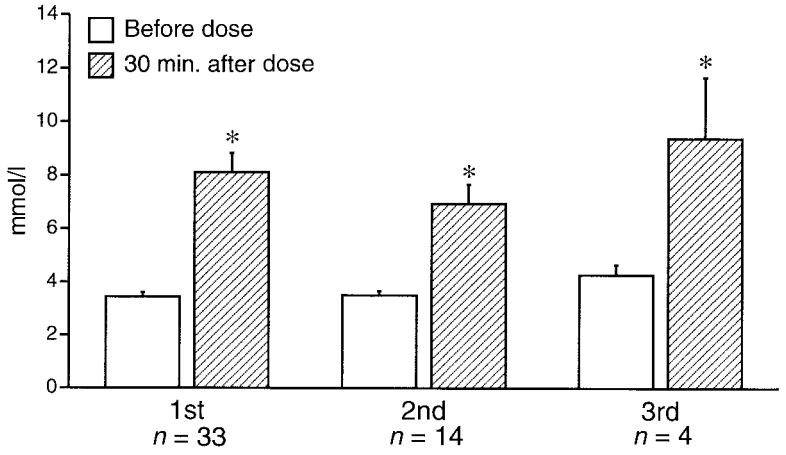

Figure 1—*Blood glucose at baseline and 30 min after mini-dose glucagon rescue in children with pending hypoglycemia associated with gastroenteritis or refusal to eat. Data are means ± SE. 1st, 2nd, and 3rd refer to the first, second, and third doses of glucagon given over the course of the children's episodes;* n *refers to the number of children receiving this dose of glucagon.* *P < *0.01.*

episodes ~4–5 months apart over this same period of time.

Statistical comparisons were made using a paired Student's *t* test. All data are expressed as means ± SE.

RESULTS — The mean age of the patients was age 6.6 ± 0.7 years (range, 1 patient age 10–12 years to 17 patients ages 11–12 years) with a mean duration of diabetes of 1.9 ± 0.5 years (range, 1 patient at 1 month to 13 patients at 11–12 years). Of the 33 episodes of impending or mild hypoglycemia, 28 were the result of gastroenteritis, characterized by nausea and vomiting (in some patients accompanied by fever and/or diarrhea). In the remaining 5 episodes, the children refused to eat or drink at a time when their blood glucose was relatively low. Of these 5, 3 were ages 3.0–3.5 years and 2 were age 10 years. The initial episode of impending hypoglycemia was treated with glucagon 6.4 ± 0.9 h (range 1.5–24 h) from the patient's last insulin injection.

Glycemic response

Glycemic response for the 33 subjects is shown in Fig. 1. At the time of the initial administration of glucagon, blood glucose was 3.44 ± 0.15 mmol/l (range 1.33–5.56; $n = 33$); 30 min after glucagon administration (6.5 ± 0.7 units [65 ± 7 μg]), blood glucose increased to 8.11 ± 0.72 mmol/l (range 5.44–24.5; $P < 0.001$). In only two children, both with gastroenteritis (ages 3 and 12.7 years), was it necessary to double the initial dosage because blood glucose failed to rise (3.11 [baseline] to 3.16 [30-min] and 3.28 [baseline] to 3.33 [30-min] mmol/l, respectively) over the initial 30 min. In one case, the last insulin dose was 2 h before the glucagon, and in the second, it was 4 h before the glucagon. In these two children, the larger dose of glucagon increased their blood glucose from 3.16 to 5.83 and 3.33 to 6.27 mmol/l, respectively. In 14 other children, the glucose subsequently decreased to 3.48 ± 0.18 mmol/l (range 2.44–5.33), but again increased to 6.94 ± 0.72 mmol/l (range 4.17–13.9; $P < 0.01$) after administration of a second dose (7.0 ± 1.5 units of glucagon). In 4 of those 14 children, the glucose once again decreased to 4.27 ± 0.40 mmol/l (range 3.11–4.94), but then increased to 9.39 ± 2.28 mmol/l (range 5.44–15.9; $P < 0.01$) after administration of a third dose (5.8 ± 1.9 units of glucagon). In the children ages <5 years ($n = 15$), the blood glucose increased from 3.27 ± 0.22 to 8.67 ± 1.39 mmol/l after the initial dose of glucagon, whereas in the children ages 5–10 years ($n = 12$) and >10 years ($n = 6$), it increased from 3.61 ± 0.28 to 8.28 ± 0.28 and from 3.50 ± 0.28 to 6.39 ± 1.28 mmol/l, respectively.

Outcomes

In no instance was acute nausea or vomiting reported by the parents immediately after the glucagon injection, despite ongoing gastroenteritis in most cases. In 28 of the 33 patients, the child remained at home and fully recovered. Five were referred to their local emergency ward because of concerns about dehydration secondary to ongoing vomiting and/or diarrhea or for fever, but none because of hypoglycemia.

CONCLUSIONS — This report provides evidence that small doses of glucagon have great utility in the management of impending hypoglycemia in children and adolescents (and possibly adults) with gastroenteritis or poor oral intake of carbohydrates. Glucagon, in dosages of 20–150 μg, resulted in an average increase in blood glucose of 3.33–5.00 mmol/l within 30 min of its administration, with a duration of effect of ~60 min. In half of the children, the plasma glucose was subsequently maintained in an acceptable range. For 14 children it was necessary to give a second dose over the course of their illness. Given in these dosages, subcutaneous glucagon did not result in a perceived worsening of the patient's nausea, and in none of these individuals did it result in emesis immediately after glucagon administration, as is commonly observed with the recommended single large (500–1,000 μg) dose. In each case, the plasma glucose was maintained in an acceptable range over the peak action times of the administered insulin.

The relative hypoglycemia observed was presumably the result of insulin's effects of decreasing hepatic glucose release and increasing peripheral glucose utilization (2). The hyperglycemic effect of glucagon is solely the result of increased hepatic glucose production (3,4), as no peripheral effect of glucagon on glucose disposal has been reported. In addition, patients treated with insulin are known to have a defective glucagon counterregulatory response to hypoglycemia (5,6). Therefore the glycemic response observed in the present study strongly supports the finding that the relative hypoglycemia in these children was the result of relative hyperinsulinemia (2).

We do not know the potency of reconstituted glucagon over time, nor do we know the duration of clinical efficacy of repeated doses. However, our present and previous experiences (1) suggest that repeated administration of subcutaneous glucagon continues to have a therapeutic effect at these dosages, after five sequential administrations, and over a 25-h period of time. In addition, glycemic response observed in a 14- and 18-year-old

adolescent with 14 and 15 units of glucagon, respectively, suggest that this modality of treatment might be extended into the adult population.

In this study we used mini-dose glucagon in a very specific but not uncommon condition of relative hypoglycemia in the context of gastroenteritis or poor oral carbohydrate intake. For severe insulin reactions, we continue to advocate and use the much larger recommended dosages in children. However, our data suggests that the use, dosage, and route of administration of glucagon need to be carefully reexamined.

Acknowledgments— This work is a publication of the U.S. Department of Agriculture/Agricultural Research Service, Children's Nutrition Research Center, Department of Pediatrics, Baylor College of Medicine, Houston, Texas. The project was supported by grants from U.S. Department of Agriculture Cooperative Agreement #58-6250-6-001 and National Institutes of Health Grant R01-DK-55478-01. The contents of this publication do not necessarily reflect the views or policies of the U.S. Department of Agriculture, nor does the mention of trade names, commercial products, or organizations imply endorsement from the U.S. Government.

We want to thank professional staff of the Texas Children's Hospital Diabetes Care Center for their help and support in collecting the data for this manuscript. This includes Sheila Gunn, MD; Lefkothea Karaviti, MD, PhD; Kenneth Copeland, MD; Cindy Sanders, RN, MS, CPNP; and our nurse educators Susan Johnson, RN, MBA, CDE; Susan Donaldson, RN, CDE; Kim Mason, RN, BSN, CDE; Shannon Brow, RN, BSN, CDE; and Monica Phillips, RD, MS, CDE.

References

1. Haymond MW: Glycemic rescue using mini-dose glucagon in managing gastroenteritis in children with IDDM (Abstract). *Diabetes* 45 (Suppl. 2):264A, 1996
2. Rizza RA, Mandarino LA, Gerich JE: Dose-response characteristics for effects of insulin on production and utilization of glucose in man. *Am J Physiol* 240:E630–E639, 1981
3. Magnusson I, Rothman DL, Gerard DP, Katz LD, Shulman GI: Contribution of hepatic glycogenolysis to glucose production in humans in response to a physiological increase in plasma glucagon concentration. *Diabetes* 44:185–189, 1995
4. Tse TF, Clutter WE, Shah SD, Cryer PE: Mechanisms of postprandial glucose counterregulation in man: physiologic roles of glucagon and epinephrine vis-a-vis insulin in the prevention of hypoglycemia late after glucose ingestion. *J Clin Invest* 72: 278–286, 1983
5. Hoffman RP, Arslanian S, Drash AL, Becker DJ: Impaired counterregulatory hormone responses to hypoglycemia in children and adolescents with new onset IDDM. *J Pediatr Endocrinol* 7:235–244, 1994
6. Liu DT, Adamson UC, Lins PE, Kollind ME, Moberg EA, Andreasson K: Inhibitory effect of circulating insulin on glucagon secretion during hypoglycemia in type 1 diabetic patients. *Diabetes Care* 15: 59–65, 1992