Epipen as an Alternative to Glucagon in the Treatment of Hypoglycemia in Children With Diabetes

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OBJECTIVE — Fear of a severe hypoglycemic reaction is a major obstacle to achieving near-normal plasma glucose levels. Although parenteral glucagon is effective in treating these reactions, it is cumbersome to use, causes severe nausea, and is impractical in the school setting. Epinephrine is available as a premixed injection (Epipen) that may be used by all care providers. Using Epipen to treat hypoglycemia may be an effective, safe, and easy-to-use alternative to glucagon.

RESEARCH DESIGN AND METHODS — Ten children (age 11.7 ± 2.4 years) with type 1 diabetes were studied on two occasions. After an overnight equilibration period, hypoglycemia was induced via an insulin pump (1 mU · kg^{-1} · min^{-1}). At a blood glucose level of 2.8 mmol/l, either glucagon (1 mg) or epinephrine (0.3 mg), in random order, was administered intramuscularly and responses were monitored.

RESULTS — Plasma free insulin concentrations were similar in both studies. Plasma glucose levels increased by 1.7 ± 0.2 mmol/l (mean ± SEM) in 10 min and by 2.6 ± 0.2 mmol/l in 15 min with administration of glucagon and were not consistently increased with administration of epinephrine ($P < 0.01$). Peak glucagon concentrations after administration of glucagon were >60-fold higher than basal concentrations. After administration of epinephrine, peak epinephrine levels were 20-fold higher than basal concentrations.

CONCLUSIONS — Epinephrine does not seem to be an adequate substitute for glucagon in the treatment of severe hypoglycemia. The effectiveness of glucagon in reversing hypoglycemia and its side effects of nausea and vomiting are likely related to the markedly supraphysiologic plasma levels achieved with the standard intramuscular dose.

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S evere hypoglycemia is the most frequent and feared acute complication of treatment of type 1 diabetes during childhood. In fact, fear of a severe hypoglycemic reaction has become a major obstacle in achieving lower glycosylated hemoglobin levels with intensive treatment. Parenteral injection of 1.0 mg glucagon is the standard treatment for a severe insulin reaction (1,2), but the need to reconstitute the hormone with diluent makes it difficult to use in an emergent situation. In addition, the standard dose of glucagon is often associated with severe nausea and occasionally with vomiting, which can complicate recovery from hypoglycemia by limiting the patient's intake of oral carbohydrate. Because glucagon can only be administered by a licensed health professional in many school systems, diabetic children may be precluded from field trips and other extracurricular activities for reasons of safety.

Even though stimulation of epinephrine secretion is one of the main endogenous hormonal defenses against insulin-induced hypoglycemia in type 1 diabetes, use of epinephrine for treatment of severe hypoglycemia in children has not been tested. This is surprising because a premixed and prefilled injection system for parenteral epinephrine administration is available for treatment of severe allergic reactions (Epipen; Dey Laboratories). Due to its ease of use and absence of severe side effects, teachers, administrators, and other school personnel are permitted to use the Epipen in emergency situations. The present study was consequently undertaken to examine whether parenteral injection of epinephrine using the Epipen system could provide an effective alternative to injection of glucagon in children with diabetes.

RESEARCH DESIGN AND METHODS

Study subjects
Ten nonobese children (seven girls and three boys) with type 1 diabetes were studied. They had a mean (±SD) age of 11.7 ± 2.4 years and duration of diabetes of 46 ± 22 months. All of the patients were on a continuous subcutaneous insulin infusion and had good glycemic control with a mean glycosylated hemoglobin of 6.8 ± 0.5 (normal value <6.4). None had clinical evidence of autonomic neuropathy or severe hypoglycemia within the preceding three months, and none were receiving any medication other than insulin. The study was approved by the Yale Human Investigation Committee, and all of the subjects and their parents gave written informed consent.

Experimental protocol
Each patient was studied on two occasions separated by an interval of at least 4 weeks. On each occasion, the patient was admitted to the Yale Children's Clinical Research Center at 8:00 P.M. on the night

before the study. Each patient had eaten dinner before admission and had received the usual bolus of lispro insulin (Eli Lilly, Indianapolis, IN) for the meal. On admission, an intravenous cannula was inserted in an antecubital vein for blood sampling and the patients were maintained on their usual overnight subcutaneous basal infusion of lispro insulin. Blood glucose levels were measured hourly overnight and maintained between 3.9 and 8.3 mmol/l by giving an intravenous bolus of 20% dextrose if levels were <3.9 mmol/l and by increasing the subcutaneous infusion of insulin if levels were >8.3 mmol/l.

At 7:00 A.M. the following morning, blood samples were drawn for baseline hormone levels and the insulin infusion was then increased to 1 mU · kg^{-1} · min^{-1} and stayed at this rate for the duration of the study. During the following 60–120 min, blood glucose levels were allowed to decrease to 2.8 mmol/l. When the blood glucose concentration was 2.8 mmol/l, either 1.0 mg glucagon or 0.3 mg epinephrine (via Epipen) was administered intramuscularly in the anterolateral aspect of the thigh. The patients were then monitored for 1 h after administration of the drug. Blood samples were taken at 20- to 30-min intervals during the prehypoglycemic period and at 5- to 10-min intervals during the hypoglycemia period for measurement of insulin, glucagon, epinephrine, and norepinephrine levels. Blood glucose levels were measured at the bedside at 5- to 10-min intervals throughout the study.

Symptoms of hypoglycemia were assessed at 15-min intervals with a questionnaire in which subjects were asked to rate a set of symptoms on a scale of 0 (nonexistent) to 6 (extreme). The symptoms were difficulty concentrating, headache, thinking slow, sweaty, anxious, shaky, and pounding heart. The scores were added to give a total hypoglycemic score (possible range 0–36). Families were instructed to call the principal investigators (T.P.C.M./J.A.A.) if there was any problem after discharge from the research center. Heart rate and blood pressure were measured at 5- to 15-min intervals, and the electrocardiogram was monitored throughout the study. The order of the studies for each subject was random (randomization performed by the Investigational Pharmacy), and a Yale Children's Clinical Research Center study nurse administered the drug so that both the in-

Table 1—*Baseline and peak insulin levels during the two studies*

	Baseline		Peak insulin levels	
	Insulin dose (mU · kg^{-1} · min^{-1})	Insulin level (pmol/l)	Insulin dose (mU · kg^{-1} · min^{-1})	Insulin level (pmol/l)
Glucagon	0.3 ± 0.14	73 ± 3	1.0	152 ± 8
Epipen	0.3 ± 0.15	75 ± 7	1.0	136 ± 16

Data are means ± SEM. Peak insulin levels were achieved at the time of hypoglycemia (0 min) and were maintained throughout the study.

vestigators and the children were masked to the drug that was being given.

Analytical methods
Plasma glucose levels were measured by the glucose oxidase method with a Beckman glucose analyzer (Beckman Instruments, Brea, CA). Catecholamines were collected in ice tubes containing glutathione and measured by high-performance liquid chromatography assay. Plasma free insulin (measured after precipitation with polyethylene glycol) and glucagon were measured by double-antibody radioimmunoassays (Human Insulin and Glucagon RIA kits; Linco Research, St. Charles, MO). All samples from each subject were measured in a single assay. The intra-assay coefficients of variation for free insulin, glucagon, epinephrine, and norepinephrine were 11, 7, 6.5, and 4%, respectively.

Statistical analysis
Data in text and figures are presented as means ± SEM. The plasma glucose concentrations, hormone responses, and symptom responses in the two studies were compared by analysis of variance with repeated-measures design. When there was a significant group-time interaction, two-tailed paired Student's t test was used to localize the effects. Baseline plasma concentrations were defined as the means of the values at –120 to –30 min during the induction of hypoglycemia; 0 min is defined as the moment the blood glucose concentration was 2.8 mmol/l and the epinephrine or glucagon was given.

RESULTS — As shown in Table 1, basal free insulin levels before the increase in insulin infusion rate were nearly identical during the glucagon and epinephrine studies. In addition, when the insulin infusion rate was increased to 1.0 mU · kg^{-1} · min^{-1}, similar plateau values were

achieved and maintained in both studies. It took 101 ± 11 min (range 45–170) to induce hypoglycemia after the insulin infusion rate had been increased. The time needed to induce hypoglycemia was similar in both studies.

Basal plasma glucagon levels were similar in the glucagon (45 ± 0.2 ng/l) and epinephrine (42 ± 0.8 ng/l) studies (Fig. 1), and plasma glucagon concentrations did not change during induction of hypoglycemia. Intramuscular injection of glucagon resulted in a rapid and marked increase in plasma glucagon concentrations to 3,032 ± 420 ng/l with peak plasma glucagon values achieved 21 ± 3 min after administration of glucagon. In contrast, no change in plasma glucagon values was observed after administration of epinephrine ($P < 0.01$ for comparison between the two groups).

As shown in Fig. 1, basal concentrations and the increase in the plasma epinephrine levels that were observed during induction of hypoglycemia were similar in both studies (from 189 ± 26 to 595 ± 120 pmol/l and from 174 ± 11 to 644 ± 322 pmol/l in the glucagon and epinephrine studies, respectively). After intramuscular injection of epinephrine, plasma epinephrine levels increased to peak values that averaged 4,538 ± 578 pmol/l, and the time to peak varied between 5 and 50 min (mean 18 min). After administration of glucagon, plasma epinephrine levels returned to baseline concentrations ($P < 0.01$ for comparison between the two groups) (Fig. 1). There were no differences in plasma norepinephrine concentration between the two studies (data not shown).

Baseline plasma glucose levels were slightly higher during the epinephrine study than during the glucagon study (Fig. 1). Nevertheless, increasing the insulin infusion rate lead to a gradual decrease in
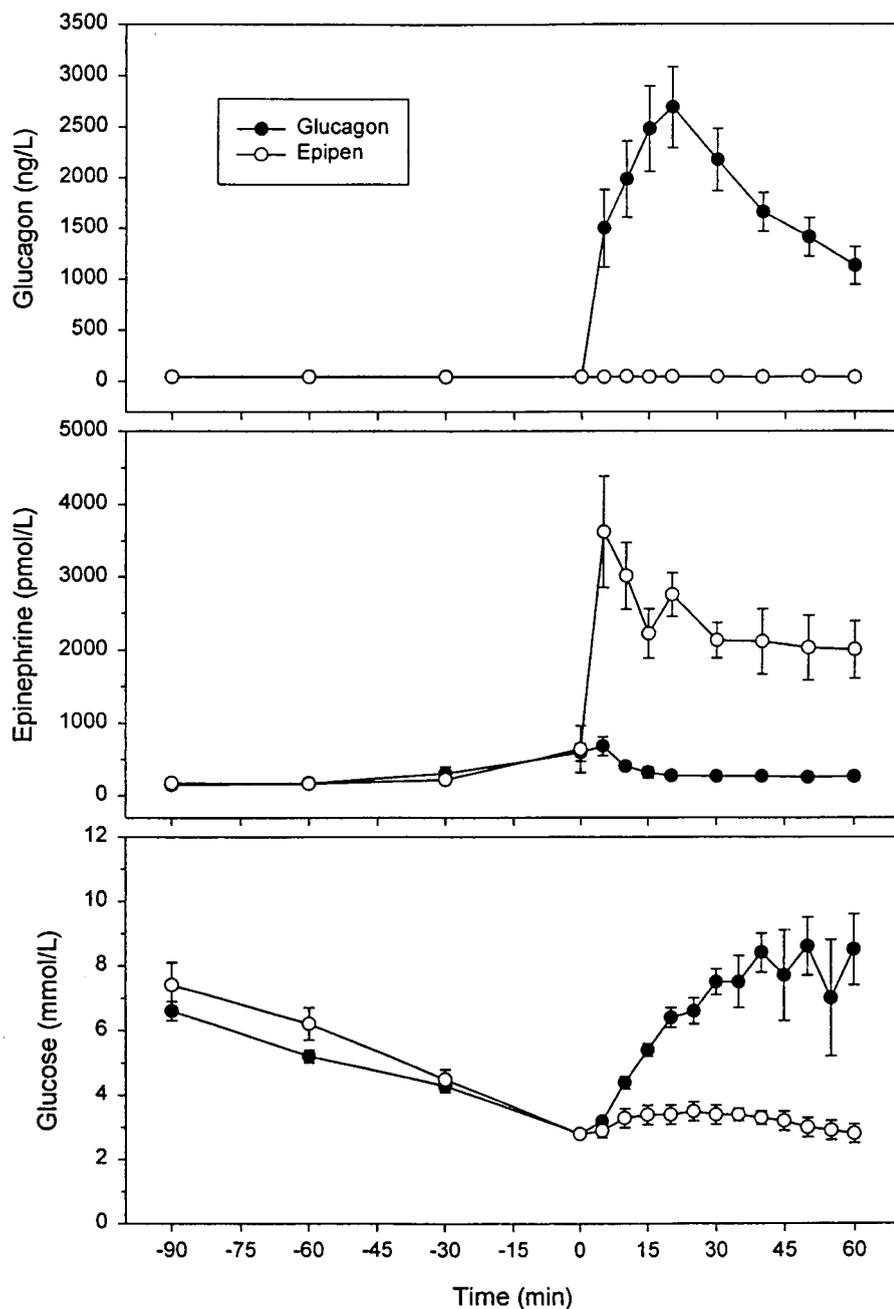
Figure 1—*Plasma glucagon, epinephrine, and glucose concentrations after administration of glucagon (●) and epinephrine (○). After hormone administration (0 min), hormone levels between the two studies differed significantly after 5 min (P < 0.01), and plasma glucose levels differed (P < 0.01) after 10 min.*

plasma glucose over ~2 h in both studies. As illustrated in the bottom panel of Fig. 1, parenteral administration of glucagon was able to rapidly reverse the decrease in plasma glucose, even in the face of ongoing insulin infusion. Plasma glucose levels, which had increased by 1.7 ± 0.2 mmol/l by 10 min and by 2.6 ± 0.2 mmol/l by 15 min, were increased to 8.5 ± 1.1 mmol/l by the end of the study. In comparison to the response to the glucagon injection, the plasma glucose response to epinephrine was disappointing. In the group as a whole, epinephrine was able to raise plasma glucose by only 0.4 ± 0.3 mmol/l at 10 min and by 0.5 ± 0.3 mmol/l at 15 min (*P* < 0.01 for comparison between the two groups). Moreover,

plasma glucose levels began to decline again after 30 min.

Four patients did show responses when given epinephrine by increases in plasma glucose levels of at least 1.1 mmol/l in 15 min. When taken separately, their plasma glucose levels were 4.3 ± 0.2 mmol/l at 15 min. In only one patient was this response sustained for 60 min. The basal and peak hormonal levels of these four patients were not significantly different within and among groups. Of note, in 4 of the 10 children, maximum plasma epinephrine concentrations were achieved by 5 min. Of these four patients, three responded to the epinephrine by an increment in plasma blood glucose levels of at least 1.1 mmol/l by 15 min.

Hypoglycemic symptom scores were higher in the patients who received the epinephrine injection (peak scores 10 ± 5 vs. 6 ± 3 for epinephrine versus glucagon, respectively; *P* < 0.01), although both groups had relatively mild symptoms (total score possible = 36). None of the patients complained of nausea immediately after receiving glucagon. However, 2–6 h after receiving the glucagon injection, 9 of the 10 patients complained of severe nausea that continued for up to 12 h. The mean heart rates increased only transiently after receiving epinephrine and peak values were within the wide range of normal values. No serious adverse effects were reported in either treatment group.

CONCLUSIONS — The present study was undertaken to determine whether a fixed dose of epinephrine using the Epipen system might serve as an alternative to glucagon in the treatment of hypoglycemia.

Although the severe hypoglycemia that occurs when the endogenous glucagon response is impaired suggests that increased catecholamine secretion does not fully compensate for defective glucagon responses (3), the hypothesis that we tested was whether administration of pharmacologic doses of epinephrine would cause recovery from hypoglycemia with only minimal side effects.

Hypoglycemia was induced in the study by a subcutaneous infusion of insulin in a dose that raised plasma free insulin levels by only about twice basal concentrations, levels that might be expected to be observed during a hypoglycemic epi-

sode. Similarly, the infusion rate was continued throughout the study to prevent the potentially confounding effects of waning plasma insulin levels on the response to the two anti-insulin hormones. This approach was also designed to simulate the persistent hyperinsulinemia that occurs during clinical hypoglycemic episodes in insulin-treated diabetic patients.

As expected, administration of the standard 1.0-mg dose of glucagon intramuscularly resulted in a prompt and substantial increase in plasma glucose from 2.8 to 8.3 mmol/l. This increase in glucose represents a pharmacologic rather than a physiologic response to glucagon, in that plasma glucagon levels that were achieved were more than 60-fold higher than basal concentrations and 15- to 20-fold higher than the endogenous glucagon response to insulin-induced hypoglycemia in nondiabetic subjects (4). It is not surprising, however, that such marked hyperglucagonemias lead to severe and prolonged nausea in many of the children in this study. Smaller doses of glucagon have been used to prevent hypoglycemia during sick days with apparent success and no reported nausea (5). It remains to be determined whether smaller doses of glucagon would also be equally effective and better tolerated in young patients during severe hypoglycemic episodes.

Compared with glucagon, intramuscular injection of epinephrine via Epipen was much better tolerated by the children in this study. The patients reported mild adrenergic symptoms and heart rate increased only slightly. Unfortunately, the Epipen injection was also much less effective than glucagon in reversing insulin-induced hypoglycemia. In this study, the Epipen injection counteracted the decrease in plasma glucose levels but did not reverse hypoglycemia. Even in the subjects who showed the best responses, plasma glucose increased by only 1.4–1.9 mmol/l, an increment that might be insufficient to correct more severe hypoglycemia seen in clinical practice. Thus, use of the Epipen in the single-dose form that is presently available does not seem to be an adequate alternative to glucagon in the treatment of severe hypoglycemia.

The symptomatic effects of increased sympathoadrenal activity provide an early warning of hypoglycemia and facilitate the ingestion of carbohydrate (6). Catecholamines also have very powerful anti-insulin effects, including suppression of endogenous insulin secretion, inhibition of glucose consumption in extraneural tissues, generation of alternate fuels by stimulation of lipolysis, and generation of gluconeogenic precursors from peripheral energy stores (6). Therefore, the weak plasma glucose response to epinephrine in our patients was surprising. The Epipen injection failed to reverse hypoglycemia, even though the increase in plasma epinephrine levels was very rapid and peak concentrations (i.e., >4,366 pmol/l) exceeded those seen during hypoglycemic clamp studies in diabetic and nondiabetic subjects (4,7). It should be noted that most of our subjects were prepubertal and all were very well controlled using insulin pump therapy. Both of these factors may have served to increase sensitivity to insulin (8) and decrease responsiveness to epinephrine. It is intriguing to speculate that decreased responsiveness to epinephrine may explain, in part, why younger age is an independent risk factor for severe hypoglycemia in clinical epidemiological studies of children with diabetes (9,10).

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