Comparison of Intravenous Glucagon and Dextrose in Treatment of Severe Hypoglycemia in an Accident and Emergency Department

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Hypoglycemia is a serious problem in insulin-treated diabetic patients. In this study the efficacy of intravenous glucagon (1 mg) was compared with that of intravenous dextrose (25 g) in the treatment of hypoglycemia in insulin-treated patients attending an accident and emergency department. In addition, the prevailing glycemic control of these patients was compared with patients routinely attending a diabetic outpatient clinic. Both intravenous glucagon and dextrose were effective in the treatment of hypoglycemic coma. There was a difference in the glycemic profile after intravenous glucagon compared with intravenous dextrose, and recovery of a normal level of consciousness after glucagon was slower than after dextrose (6.5 vs. 4.0 min, respectively; $P < .001$), although the average duration of hypoglycemic coma was 1.4 h. The glucagon- and dextrose-treated groups had significantly lower HbA_1 than comparable patients routinely attending the clinic (9.5 ± 0.8 vs. 12.0 ± 3.8%, respectively; $P < .001$). In view of the ease of administration and the small risk of vascular and extravascular complications, intravenous glucagon appears to be a useful alternative to intravenous dextrose in the treatment of severe hypoglycemia. *Diabetes Care* 10:712–15, 1987

Hypoglycemia remains a serious common complication of insulin therapy in diabetic patients. It accounts for ~4% of deaths in diabetic patients <50 yr of age (1), and several studies have shown that between 8 and 15% of insulin-treated diabetic patients experience at least one severe hypoglycemic episode each year (2–6). Although glucagon has been demonstrated to be effective in the treatment of hypoglycemia (7–10), its therapeutic usefulness has not previously been compared with that of intravenous dextrose. Therefore, we have compared the efficacy of intravenous glucagon with that of intravenous dextrose in the treatment of severe hypoglycemia in insulin-treated patients presenting at an accident and emergency department. In addition, the prevailing glycemic control of these hypoglycemic patients was compared with that of patients routinely attending the outpatient clinic (6).

MATERIALS AND METHODS

The study group consisted of 52 consecutive insulin-treated diabetic subjects with hypoglycemic coma referred to the Accident and Emergency Department, Royal Infirmary, Edinburgh, United Kingdom (Table 1). Hypoglycemia was confirmed by capillary blood, with a Boehringer Mannheim Reflocheck meter, and plasma, with a Yellow Springs glucose oxidase analyzer. After insertion of an intravenous cannula (Venflon), venous blood was withdrawn for plasma glucose and glycosylated hemoglobin (HbA_1) measurements. HbA_1 assay was by electrophoresis with commercially available agar plates; the normal range was 6–8% (11). Consciousness was assessed and graded as: 0, normal orientation in time and place; 1, drowsy; 2, maximal response to minimal stimuli; 3, minimal response to maximal stimuli; and 4, unresponsive to painful stimuli (12). Patients were then randomly allocated to emergency treatment with either intravenous glucagon (1 mg) or 50 ml 50% dextrose (25 g). After careful flushing of the Venflon, blood was taken for plasma glucose estimation at 5, 10, 15, and 30 min. The time taken for the patient to return to a normal level of consciousness was recorded. Consciousness was assessed throughout the study by the same observer, and if it was grade 3 or worse at 15 and 30 min, 12.5 g i.v. dextrose was administered. After recovery from hypoglycemia, patients were asked whether they had a headache, and it was noted whether they had

TABLE 1
Patient data on arrival at Accident and Emergency Department

	Glucagon treated (n = 25)	Dextrose treated (n = 24)
Initial plasma glucose (mg/dl)	18 (9–47)	20 (6–56)
HbA_1 (%)	9.2 ± 1.9	9.9 ± 1.7
Age (yr)	39.4 ± 17.1	40.2 ± 14.2
Duration of diabetes (yr)	14.0 (4–47.2)	13.0 (2–32.0)
Duration of hypoglycemia (h)	1.3 (0.3–4.0)	1.5 (0.3–9.0)

Results are means ± SD or medians (range) where appropriate.

vomited after the administration of glucagon or dextrose. The HbA_1 of patients attending the accident and emergency department was compared with the age, sex, and duration of diabetes of a comparable group of patients (n = 504) routinely attending the diabetic department (6).

After the patients had returned to a normal level of consciousness, a questionnaire was completed by the patients and their relatives and friends present. Details including age, duration of diabetes, insulin dosage, and the most likely precipitating cause and an estimate of the duration of the hypoglycemic episode were established. Patients were asked about the usual causes of hypoglycemia and what steps were taken to try to abort the episode. In addition, patients and their relatives or friends were asked about their knowledge of glucagon and its role in the treatment of hypoglycemia.

Of the 52 referrals entered into the study, 3 had a repeat hypoglycemic episode; only their first visit was considered for statistical analysis. In addition, a diabetic patient with coexisting Addison's disease was also excluded from statistical analysis. The glucagon- and dextrose-treated groups were compared with t tests or Wilcoxon ranked-sums tests where appropriate. An unpaired t test was used to compare the HbA_1 of the entire group requiring treatment for hypoglycemia with that of a comparable group of patients routinely attending the clinic. The protocol was approved by the local Hospital Advisory Ethical Committee.

RESULTS

The glucagon-treated (n = 24) and dextrose-treated (n = 24) groups were comparable in terms of initial blood glucose, prevailing glycemic control (HbA_1), age duration of diabetes, and duration of hypoglycemia (Table 1). However, there was a significant difference in the subsequent glycemic profiles between the patients treated by intravenous glucagon compared with those treated by intravenous dextrose (Fig. 1). The group treated with glucagon was slower to achieve normal conscious level (median 6.5 min, range 2–16 min) than the group treated with dextrose (median 4 min, range 1–15 min; $P < .001$). All patients recovered a normal level of consciousness within 30 min of arrival at the accident and emergency department. There was no correlation in either the glucagon- or dextrose-treated groups between presenting plasma glucose or duration of hypoglycemia and the time to reach a normal level of consciousness. The glucagon- and dextrose-treated groups together had significantly lower HbA_1 (mean ± SD) than the comparable insulin-treated patients routinely attending the clinic (9.5 ± 0.8 vs. 12.0 ± 3.8%, $P < .001$).

Two patients in both the glucagon- and dextrose-treated groups required further (12.5 g i.v.) dextrose. The patient with Addison's disease received intravenously both glucagon and dextrose but returned to a normal level of consciousness only after hydrocortisone administration. Eight patients in the glucagon-treated group vomited compared with 9 in the dextrose-treated group. Thirteen patients in the glucagon-treated group experienced headaches on return to a normal level of consciousness compared with 12 in the dextrose-treated group.

A clear precipitating cause for hypoglycemia was often difficult to elicit, and no obvious cause was found for 30% of the episodes. Twelve patients had missed a meal, which was a clear precipitant of the hypoglycemic episode. Ten patients were considered to have an irresponsible attitude toward control of their diabetes (4); e.g., none of this group undertook monitoring of blood or urine glucose. Three patients developed hypoglycemic coma with blood alcohol levels >100 mg/dl, and 1 patient became hypoglycemic as a result of marked fluctuations of insulin requirements secondary to pregnancy (Table 2). Thirty-six patients were fully aware of the usual causes of hypoglycemia, but only 21 had attempted to reverse it. Twenty-three patients had heard of glucagon, whereas only 12 kept it at home or work. Forty-one had relatives or friends who would have been available to administer it if necessary. One patient received subcuta-

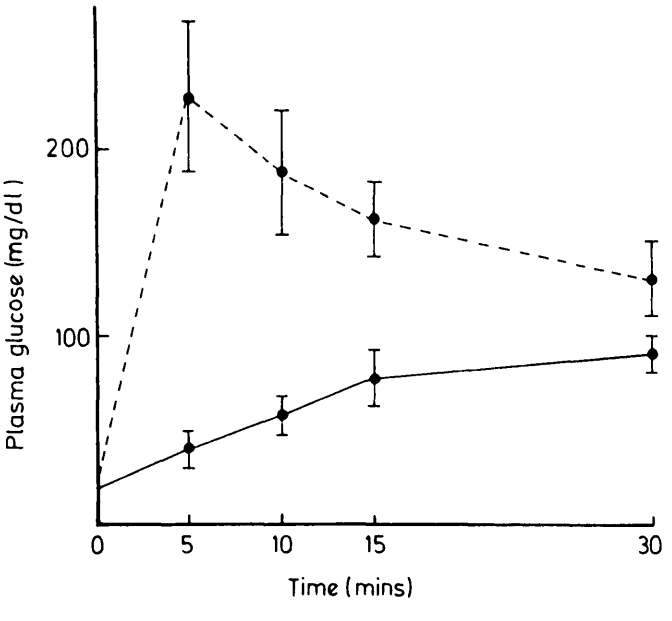

FIG. 1. Glycemic profiles after glucagon (*solid line*) and dextrose (*dashed line*) expressed as means with 95% confidence limits.

TABLE 2
Main factors precipitating hypoglycemia

	n
No obvious cause	15
Missed meal	12
Irresponsible attitude	10
Exercise	7
Excessive alcohol intake	3
Pregnancy	1
Addison's disease	1
Total	49

neous glucagon administered at home by a relative. Her plasma glucose on arrival at the accident and emergency department was 56 mg/dl (compared with mean initial plasma glucose of 18 mg/dl), and she had borderline grade 3 level of consciousness.

DISCUSSION

This study confirmed that glucagon is effective in the treatment of severe hypoglycemia, giving a predictable rise in plasma glucose (7–10). Although the return to a normal level of consciousness was slower than with dextrose, the difference was small (2.5 min), especially when compared with average duration of hypoglycemia experienced by these patients (1.4 h). Vomiting and headache were common after recovery from hypoglycemia, with no difference between the glucagon- and dextrose-treated groups. Although nausea is a recognized side effect of glucagon therapy (13), vomiting probably occurred secondary to hypoglycemic coma, possibly as a result of irritation of the vomiting center by neuroglycopenia or cerebral edema (14). Hypoglycemia-induced parasympathetic discharge that alters gastric motility may be a further contributory factor (15). In addition, the headache experienced by ~50% of the patients was probably due to neuroglycopenia (14).

Because of the hope of delaying or preventing diabetic complications, meticulous glycemic control is an important goal of diabetic patient education (16). However, this study suggests that patients with HbA_1 closer to the nondiabetic range are at greater risk of severe hypoglycemia. It is possible that some of the patients had inappropriately low HbA_1 levels due to unrealistic therapeutic goals. Patients with defective counterregulatory hormonal mechanisms are, of course, at particular risk of hypoglycemia and should aim for less stringent HbA_1 values (17). In addition ~25% of the patients complained that they had little or no hypoglycemia warning symptoms. Therefore, the application of meticulous glycemic control should involve careful patient selection combined with intensive education and close self-monitoring to avoid significant hypoglycemia.

The education of relatives and friends in the use of subcutaneous and intramuscular glucagon injections for hypoglycemia is becoming an integral part of diabetes training programs (6,10). Both subcutaneous and intramuscular glucagon have glycemic responses essentially comparable to the intravenous route of administration (10), and their use in the home or workplace has been shown to reduce emergency hospital attendance (6). In this study, <50% of the patients had heard of glucagon, which is comparable to glucagon awareness in patients routinely attending the clinic (6). Because most patients had relatives or friends who would have been available to administer glucagon if necessary, it is possible that a significant number of the emergency hospital attendances could have been avoided if glucagon had been readily available at either home or work.

Although glucagon is possibly less effective in the presence of impaired liver function (18), intravenous glucagon appears to be a useful alternative to intravenous dextrose in the treatment of severe hypoglycemia in hospital accident and emergency departments. In addition, glucagon has several potential advantages, being easy to administer with little risk of intravenous thrombosis or extravascular complications (8).

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