Comparison of intramuscular glucagon and intravenous dextrose in the treatment of hypoglycaemic coma in an accident and emergency department

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SUMMARY

Hypoglycaemia remains a serious and much feared complication of insulin therapy. In this study, patients attending an accident and emergency department in hypoglycaemic coma were randomized to treatment with either intravenous dextrose (25g) or intramuscular glucagon (1mg), administered into the right thigh. Restoration of normal conscious level was slower after glucagon than dextrose (9.0 vs 3.0 min, $P < 0.01$), although the average duration of hypoglycaemic coma was 120 min. Two patients in the glucagon-treated group, who failed to show satisfactory recovery after 15 min, required additional treatment with intravenous dextrose. On questioning following recovery, all except two patients reported loss of awareness of the onset of hypoglycaemia.

Intramuscular glucagon is valuable in the treatment of severe hypoglycaemia outwith hospital and, although the slightly slower and less predictable recovery may appear to make it a less attractive option than intravenous dextrose in the accident and emergency department, this must be balanced against the advantages of ease of administration and a lower incidence of serious adverse effects.

INTRODUCTION

Hypoglycaemia remains a significant cause of mortality in diabetics (Tunbridge, 1981) and up to 13% of patients treated with insulin will experience at least one severe hypoglycaemic episode each year (Potter *et al.*, 1982; Casparie & Elving, 1985;

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Matthews *et al.*, 1986). Intravenous dextrose continues to be widely used by medical staff to treat hypoglycaemia but intravenous glucagon has been shown to be an effective alternative (Collier *et al.*, 1987), with a low risk of intravenous thrombosis or extravascular complications (Shipp *et al.*, 1964; Collier *et al.*, 1987). To date, however, other routes of administration of glucagon have not been compared with intravenous dextrose, although glucagon, administered intramuscularly or subcutaneously, is increasingly used by families and friends of diabetic patients to treat severe hypoglycaemia at home or work.

METHODS

The study group consisted of 29 insulin-treated diabetic patients, presenting consecutively to the Accident and Emergency Department, Royal Infirmary, Edinburgh, Scotland with hypoglycaemic coma. Hypoglycaemia was confirmed on a capillary blood specimen using a Reflolux II Meter (Boeringer Mannheim, Mannheim, FRG) and patients were randomly allocated to treatment with either 50 ml 50% dextrose intravenously or 1 mg glucagon intramuscularly, administered into a defined site in the right thigh. Venous blood was withdrawn prior to treatment for measurement of plasma glucose, alcohol and glycated haemoglobin, with further samples being taken after 5, 10, 15 and 30 min for plasma glucose estimation. Time taken to recover normal conscious level was noted and a further 12.5 g of dextrose was given intravenously if satisfactory clinical recovery had not occurred 15 min after treatment. Following recovery, patients, and any relatives or friends present, were questioned to determine the duration of hypoglycaemia prior to treatment, although in several cases it was only possible to obtain a rough estimate of this. Details were obtained of insulin and other drug therapy, in addition to possible precipitating causes or any preceding loss of awareness of the onset of hypoglycaemia.

Students T-tests or Wilcoxon ranked sum tests were used, as appropriate, to compare the two treatment groups. The study protocol was approved by the local Hospital Advisory Ethical Committee.

RESULTS

The glucagon- ($n=15$) and dextrose-treated ($n=14$) groups were not significantly different in terms of age, duration of diabetes, initial plasma glucose, glycated haemoglobin or estimated duration of coma (Table 1). Glycaemic profiles following treatment with dextrose and glucagon were however significantly different (Fig. 1) and the glucagon-treated group was slower to achieve normal conscious level (9 (5–30) min) than the dextrose-treated group (3 (2–15) min); $P<0.01$. Two of the glucagon-treated group, but none of the patients who received dextrose, required administration of additional intravenous dextrose on account of failure to show signs of clinical recovery within 15 min of treatment. There was no correlation between the time taken to recover

Table 1 Patient data for glucagon- and dextrose-treated groups.

	Glucagon-treated group (n = 15)	Dextrose-treated group (n = 14)
Sex	12 M: 3 F	10 M: 4 F
Age (yr)	47 (17)	48 (17)
Duration of diabetes (yr)	19 (2–33)	20 (3–31)
Initial plasma glucose (mmol l ⁻¹)	1.3 (0.5)	1.2 (0.5)
Glycated haemoglobin (%)	9.7 (1.9)	9.6 (1.7)
Duration of coma (min)	120 (60–240)	120 (20–480)

Mean (SD) or median (range) as appropriate.

Fig. 1 Glycaemic profiles after glucagon (solid line) and dextrose (dotted line) expressed as means (SD). Significant differences between two values are indicated by *.

consciousness and either the initial plasma glucose concentration or the duration of hypoglycaemia.

A clear precipitating cause for the episode of hypoglycaemia was often not apparent and, in particular, alcohol was only detected in the plasma of three patients, with the highest level recorded being 3 mmol l⁻¹. Nineteen patients were on treatment with a twice daily mixture of soluble, and isophane or lente insulins. The remaining 10 patients were receiving once daily lente or protamine zinc insulins, either with or without additional soluble insulin before breakfast. All except one patient in each group reported either partial or total loss of awareness of the onset of hypoglycaemia, but none were receiving treatment with beta blockers or other drugs which might alter hypoglycaemic awareness or affect the counterregulatory response.

DISCUSSION

Our results confirm the findings of others (Elrick *et al.*, 1958; Shipp *et al.*, 1964; Aman & Wranne, 1988), in demonstrating that intramuscular glucagon is effective in restoring the plasma glucose level towards normal, even following prolonged hypoglycaemic coma, as was the case in many of the patients reported in the present study. The rate of recovery was, however, slower than that reported following intravenous glucagon in a similar study in an accident and emergency department (Collier *et al.*, 1987) and this finding might be expected on the basis of previous research into the pharmacokinetics of glucagon, with higher plasma levels being obtained during the first 15 min after intravenous glucagon in comparison with either intramuscular or subcutaneous administration (Muhlhauser *et al.*, 1985). In the present study, the difference between the median recovery times of the groups treated with intravenous dextrose and glucagon (6 min), although statistically significant, was however small in comparison with the average duration of hypoglycaemic coma (120 min). It is probably of more importance that two patients in the glucagon-treated group required additional therapy with intravenous dextrose. These patients could not have been predicted in advance on the basis of the initial plasma glucose level or duration of coma, and nor was there any evidence of preceding alcohol intake or hepatic disease, which might have affected the clinical response to glucagon.

When questioned following recovery, it was striking that all except two of the patients in the study reported at least partial loss of hypoglycaemic awareness. It has previously been shown that patients with glycosylated haemoglobin levels closer to the non-diabetic range are at greater risk of hypoglycaemia (Matthews *et al.*, 1986; Collier *et al.*, 1987) and tight glycaemic control, as present in several of our patients, is known to be associated with reduced awareness of the onset of hypoglycaemia, in addition to impaired glucose counterregulatory responses (Amiel *et al.*, 1987). It is likely, however, that the long average duration of diabetes (20 yrs) is also a significant factor in explaining the loss of awareness in many of the group reported here.

Although the rather slower and less predictable recovery rate following intramuscular glucagon may appear to make this a less attractive alternative to intravenous dextrose in the treatment of severe hypoglycaemia in the specific setting of the accident and emergency department, this has to be weighed up against the advantages of ease of administration and absence of the intravenous and extravascular complications associated with the use of concentrated dextrose solutions.

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