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Glucagon for metabolic/endocrinologic emergencies: hypoglycaemia

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I. THE PROBLEM OF HYPOGLYCAEMIA IN EMERGENCY MEDICINE

The high frequency of acute hypoglycaemia as a medical emergency has been well documented[1]. Hypoglycaemia has been related to approximately 4% of the deaths of elderly diabetic patients; between 8 and 15% of insulin treated diabetics experience at least one severe hypoglycaemic episode each year[2,3,4]. Excess administration of exogenous insulin or oral hypoglycaemic agents are by far the most common causes. However, severe hypoglycaemia in association with acute and chronic alcoholism, severe hepatic and renal dysfunction, endocrinologic tumours, and malnutrition are all well described[5,6,7]. Although brief periods of hypoglycaemia are ordinarily well tolerated, it is clear that prolonged severe hypoglycaemia can lead to permanent neurologic sequelae, seizures and even death[8,9,10]. The term hypoglycaemia, as utilized in this chapter and in much of emergency medical practice, refers to a symptom complex associated with subnormal glucose levels. Although chemical hypoglycaemia is often defined as a serum glucose level of 45 mg/dl or less, levels of 35 mg/dl or lower are asymptomatic in certain populations, particularly in women and neonates[11,12]. Hypoglycaemia may be clinically classified as either mild or severe; the distinction in this case is made on the ability of the patient to self-correct the problem through the enteral route. Severe hypoglycaemia is defined as when the alteration in mental status is

severe enough that parenteral therapy is required. It should be noted that severity of symptoms is related not only to the degree of depression of the serum glucose level but also to the rapidity of the fall in that level. This implies that symptomatic and even severe hypoglycaemia may occur in the presence of serum levels in the 40–80 mg/dl range[13].

The treatment of acute hypoglycaemia would appear to be straightforward, considering that the levels of serum glucose and consciousness can ordinarily be rapidly returned to normal with the infusion of hypertonic dextrose solutions. However, there are several factors that limit this approach and certain circumstances make an alternate therapeutic regimen attractive. Perhaps most obvious of these is the inability to secure intravenous access. In the medically attended setting this is most frequently due to a lack of available peripheral intravenous sites, unfortunately a common condition, particularly in chronically ill diabetic patients[14]. Although central venous cannulation can be achieved, it appears that such a procedure carries an approximate 10% complication rate. Such access may be difficult or impossible to obtain in the patient with a gravely altered mental status who is combative or who is actively seizing[15]. In the vast majority of situations where medical attendance is not immediately available, the ability to correct the hypoglycaemic state through either enteral or non-intravenous parenteral injections would be highly desirable and could be expected to obviate the need for many emergency department visits.

Two additional hazards are associated with the intravenous infusion of 50% (or 25%) dextrose. First, such solutions are both hypertonic and acidotic, frequently resulting in pain and tissue damage if extravasated[16]. Second, the rise in glucose may be quite significant; as much as 370 mg percent after one infusion[17]. A correlation exists between poor neurologic outcome and marked hyperglycaemia in the face of cerebral ischaemia such as is likely to occur in the setting of a stroke or a transient ischaemic attack (both situations in which D50 is likely to be used). Consequently a method of providing reliable, but not excessive, elevations in glucose would be desirable. In the out-of-hospital setting, establishment of an intravenous line prolongs the total prehospital time by an estimated 2.7 to 11.0 minutes, and this would no doubt be longer for a combative patient[14]. In addition, field-initiated intravenous lines have been shown to carry a higher risk of infection. It also seems likely that they would be more tenuous and prone to extravasation than lines started in the hospital setting. Since glucose estimation through chemical dipstick analysis of patient blood is not usually available in the field, and is not infallible when it is available[18,19], it is inevitable that many patients with altered mental status will be suffering from hyperglycaemia or hyperosmolarity. Further exacerbation of the hyperglycaemic and hyperosmolar state through intravenous dextrose administration is potentially deleterious.

Enteral options

For the patient with mild hypoglycaemia the obvious and time tested option for correction of hypoglycaemia is simple ingestion of glucose-containing food. In the United States this is most frequently accomplished with the traditional 'sugar in orange juice', while in the United Kingdom 'tea and toast' is a popular remedy. Although usually effective within a relatively short period of time, one should be concerned about putting food in the stomach of individuals where the aetiology of the altered mental status is not clear and where vomiting and unconsciousness may ensue[20]. Several enteral preparations have been used in cases of hypoglycaemia: Glucola, an oral agent traditionally used in glucose tolerance testing and which contains 75 grams of glucose; granulated sugar, providing only 4 grams of glucose per teaspoon; and Lucozade, an oral solution containing 22.4% glucose utilized in the United Kingdom[21]. All of these have been used successfully, and there appears to be a general consensus that the oral route is preferable in the awake and alert patient. Other options which have been utilized in the patient with severe hypoglycaemia include gel-like glucose supplements marketed under the name Glutose and others. Unfortunately, the buccal or sublingual absorption of such preparations is inadequate, and they also present an aspiration risk. Finally, the administration of concentrated glucose solutions (most commonly 25 grams of D50 administered via nasogastric or orogastric tube) is effective in restoring serum glucose levels, but carries the unavoidable risks of nasogastric cannulation in the unconscious or semi-conscious patient[22]. It seems that no currently available enterally administered therapy provides a satisfactory means of treating the severely hypoglycaemic patient.

II. GLUCAGON IN THE EMERGENCY DEPARTMENT TREATMENT OF HYPOGLYCAEMIA

The hyperglycaemic effect of parenterally administered glucagon has been known since its isolation almost 70 years ago. Much subsequent research has established that the effects of glucagon in liver, muscle and fat tissue raise the serum glucose level, counteracting the effects of insulin. As reviewed with more detail elsewhere in this volume, the complex effects of glucagon involve both glycogenolysis and gluconeogenesis, and may have clinical relevance in the patient with severe carbohydrate and/or protein depletion. It is worth noting that endogenous glucagon production is only approximately 0.1 mg per 24 hours[23,24]. This compares with a clinical dose of 1.0 to 2.0 mg corresponding to 0.1 to 0.3 mg per kilogram when glucagon is used as a drug for the treatment of severe hypoglycaemia. Although the general effect of such doses of glucagon in reversing the hypoglycaemic state has been

known and used for 30 years, it is only in the last decade, particularly in the last 5 years, that more detailed, quantitative information has been obtained on the response to varying doses of glucagon administered by different routes.

Following Elrick *et al.*'s important article presenting evidence that glucagon was effective for treating insulin reactions[25], Davies reported utilizing glucagon therapeutically in a single case of a severe chlorpropamide overdose in which the blood sugar level was not normalized despite large and prolonged intravenous and intragastric infusions of dextrose[26]. After more than 40 hours, 1 mg of glucagon was administered by intramuscular injection and repeated thereafter every 2 hours times four. This prompted an immediate rise in blood sugar and led to the conclusion that severe cases of sulphonylurea overdose might require glucagon to restore normoglycaemia. In a 1964 study of young campers, Shipp *et al.* compared glucagon to oral glucose concluding that glucagon was effective when given subcutaneously in either a 1 mg or 2 mg dose[27]. By 1979 several authors had recommended the use of glucagon in hypoglycaemia after specifying without a clear rationale the intramuscular or intravenous route[27,28,29]. In 1978, however, Taylor *et al.* studied the response to 1 mg doses of glucagon given intravenously and intramuscularly to healthy volunteers and to patients with newly diagnosed late onset nonketotic diabetes (Figure 1)[30]. They found that the maximum glucose elevation and the total area under the curve, representing total glucose elevation, was greater in patients treated intramuscularly than in those receiving the intravenous hormone. Taylor *et al.* speculated that the intravenous route led to glucagon concentrations far in excess of those required to produce maximal glycogenolysis and gluconeogenesis and, because of the short half-life of the circulating glucagon, that hormone concentrations could fall rapidly. On the basis of such data, clinicians adopted the authors preference for intramuscular rather than intravenous administration of glucagon. It should be noted that as the patients involved were normoglycaemic, the results could not necessarily be extrapolated to the hypoglycaemic population (Figure 1).

In 1985, Mühlhauser *et al.* researched the pharmacokinetics of intramuscular, subcutaneous and intravenous administration of glucagon in non-diabetic men rendered hypoglycaemic through insulin injection[1]. The results, which carefully quantified the levels of serum glucagon and glucose, indicated little difference in either measurement when comparing subjects receiving subcutaneous injection to those receiving intramuscular injection. The data indicated a maximum rise in serum glucose occurring approximately 30 minutes post-intramuscular or subcutaneous injection. In the intravenous group, however, the glucagon levels were significantly higher within the first 15 minutes after injection when compared to the other two arms of the study (Figure 2). Although the serum glucose rise was more rapid in the intravenous group, the maximum level of blood glucose was not significantly different. Mühlhauser

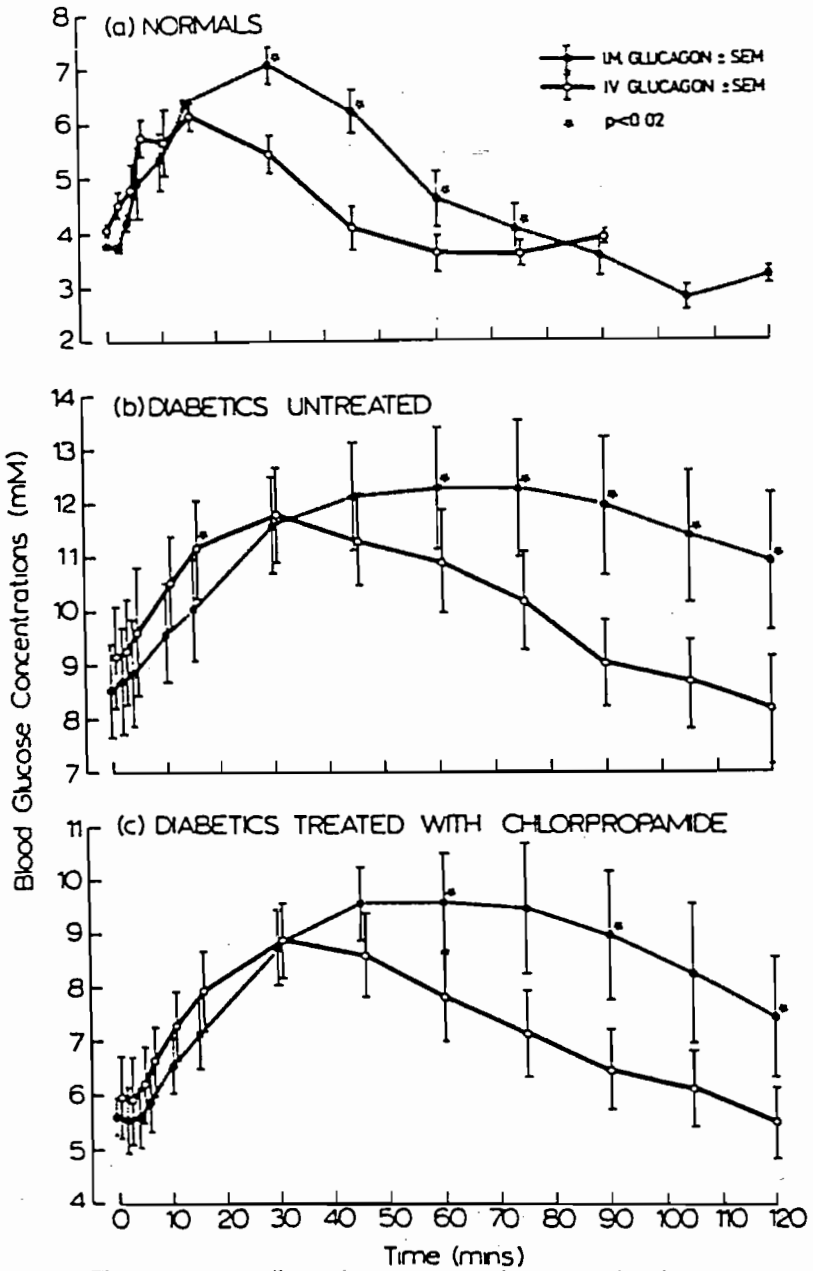

Figure 1 The comparative effects of intravenous and intramuscular glucagon injection on blood glucose concentration in normals (a), untreated diabetics (b), and diabetics treated with oral hypoglycaemic agents (c)[30].

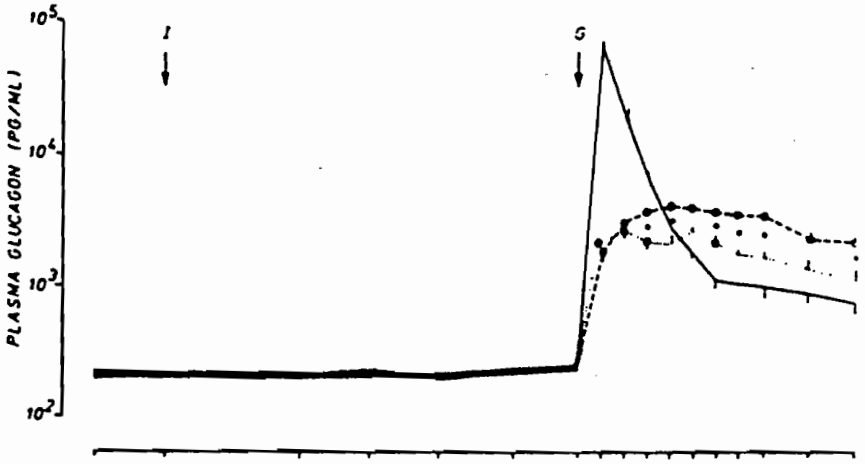

Figure 2 Plasma glucagon levels in non-diabetic volunteers after injection of 10 U regular insulin (I, at 0 minutes) and 1 mg of glucagon (G, at 90 minutes). The solid line represents intravenous administration; the dashed line intramuscular dosing, and the dotted line subcutaneous dosing. Note the statistically significant (*) but small difference between intramuscular and subcutaneous administration and large early difference between these two routes and the intravenous one[31].

et al. concluded that a maximal rapid effect would occur with an intravenous injection but that clinically there would be no difference when hypoglycaemic patients were treated with the intramuscular or subcutaneous routes.

In another large clinical study again in 1985, Mühlhauser *et al.* utilized home glucagon injections (subcutaneous or intramuscular) in an 18 month long consecutive series of 434 adults[31]. Fifty-three severe hypoglycaemic episodes were treated with injections of 1 mg of glucagon by the patients' relatives with therapy being successful in all but one case (98% success rate). In four cases a second 1 mg injection of glucagon was administered and there were three additional cases in which glucagon treatment was reported effective but consciousness was regained only after an estimated 15 minutes. The time lapse was reported by the patients' relatives. The authors noted that 'despite the obvious effectiveness of glucagon injections by relatives in cases of severe hypoglycaemia, glucagon was not administered in 30–40% of the cases, although relatives were present when loss of consciousness occurred.' Further investigation revealed that failure to administer glucagon in 34% of the cases was related to excessive anxiety on the part of the relative despite an educational program designed to encourage glucagon use in such circumstances.

Other studies in 1985 and 1987 differed in design and intent but similarly reported the successful use of glucagon in large series of diabetic patients

suffering from severe hypoglycaemia[32,33]. In these studies there was an annual rate of approximately 10% severe hypoglycaemic reactions in the insulin treated diabetics. It is worth noting, however, that the actual number of hypoglycaemic events are not entirely clear as a potential exists for both over-reporting (patients being treated by over-anxious relatives on the basis of symptoms, without laboratory documentation), and under-reporting (patients suffering from amnesia and/or neglecting to report a treated hypoglycaemic episode at their next visit). Taken together, however, studies through the mid-80's firmly established that severe hypoglycaemic reactions were fairly common in both adult and paediatric outpatients with insulin-dependent diabetes, and intramuscular or subcutaneous injection of 1 mg of glucagon by either relatives or medical personnel was a highly reliable method of restoring normoglycaemia or a slight hyperglycaemia within approximately 15 minutes.

Intravenous glucagon and dextrose

Although the effectiveness of intramuscular and subcutaneous glucagon for the treatment of hypoglycaemia was documented by the middle of the past decade, it was not until 1987 that the first comparison of glucagon and intravenous D50 appeared. Collier *et al.* first compared intravenous glucagon (1 mg) with intravenous dextrose (25 g of D50) in hypoglycaemic insulin-treated patients in the emergency department setting[32]. Their 49 consecutive patients were randomized to one of the two treatment arms. Both groups were highly comparable in terms of initial blood glucose (18–20 mg/dl), glycaemic control as measured by HbA_1 levels (9.2–9.9%), age (39.4–40.2 years) and duration of hypoglycaemia (1.3–1.5 hours). However, there was a significant difference in the subsequent glycaemic profile between the patients treated by intravenous glucagon compared with those treated by intravenous dextrose. The glucagon treated group was slower to achieve normoglycaemia and also normal consciousness (median 6.5 minutes, range 2–16 minutes) than the dextrose group (median 4 minutes, range 1–15 minutes) (Figure 3). However, all patients recovered a normal level of consciousness within 30 minutes of arrival in the emergency department and no correlation was noted in either group between presenting plasma glucose or duration of hypoglycaemia and the time needed to reach a normal level of consciousness. It was originally noted that both glucagon and dextrose treated groups had significantly lower HbA_1 levels than comparable insulin treated patients attending the same clinic (9.5 *versus* 12.0, $p < 0.001$). This most likely reflects the increased risk of severe hypoglycaemic reactions that a tight control of blood glucose entails. Two patients in each group were given an additional dextrose treatment (12.5 g intravenous). One of these patients was suffering from Addison's disease and returned to a normal level

of consciousness only after glucocorticoid administration. Details regarding history of glucose levels were not presented for the other three treatment 'failures'. There were no evident differences in the side effect profile. Vomiting was reported in 8 of the glucagon treated patients compared with 9 in the dextrose treated group. Similarly, 13 patients in the glucagon group experienced headaches after return to normal consciousness compared with 12 in the dextrose group. Additionally it was noted that 23 of the total 49 patients in this large university hospital emergency department (Royal Infirmary, Edinburgh, United Kingdom) had heard of glucagon and 12 of them kept it at home or at work. Thirty-one of the 49 (82%) patients stated they had relatives or friends who would have been available to administer the agent. The authors conclude that intravenous glucagon, like subcutaneous and intramuscular glucagon, is adequate in giving a predictable rise in plasma glucose. Although the return to a normal level of consciousness was slower than with dextrose, the difference (2.5 minutes) was small, particularly when compared with the average duration of hypoglycaemia (1.4 hours) experienced by these patients. Side effects (nausea, vomiting and headache) appeared to be related to the hypoglycaemic or neuroglycopenic state itself rather than to the solutions utilized.

The more clinically relevant study comparing intramuscular glucagon to intravenous dextrose appeared in 1990. Patrick *et al.* compared these two regimens (glucagon 1 mg intramuscular *versus* D50 25 g intravenous) in 29 consecutive insulin treated diabetics in a United Kingdom urban emergency department[34]. Hypoglycaemia was confirmed prior to therapy, and the patients were randomly allocated to one of the two treatment groups. Consecutive samples were taken for glucose measurement and HbA_1 and alcohol levels. Recovery time to normal conscious level was reported and, as in the previous study, 12.5 g of dextrose was given intravenously if satisfactory clinical response had not occurred within 15 minutes. As in the intravenous study done several years earlier, the two groups were similar in terms of baseline characteristics. However, glycaemic profiles following treatment with dextrose and glucagon were significantly different. There was a more gradual return to normoglycaemia and an absence of severe hyperglycaemia in the glucagon-treated group (Figure 4). The similarity to Figure 3 is notable.

In terms of return to normal consciousness, the glucagon treated group was slower (9 minutes, range 5–30 minutes) than the dextrose treated group (3 minutes, range 2–15 minutes), where $p < 0.01$. Moreover, two of the patients in the glucagon treated group, but none of the D50 patients, required administration of additional intravenous dextrose at the conclusion of the 15 minute post-therapy time point. Neither initial plasma glucose nor the duration of hypoglycaemia correlated with the time taken to recover full consciousness. The authors emphasized that although the median recovery time of the

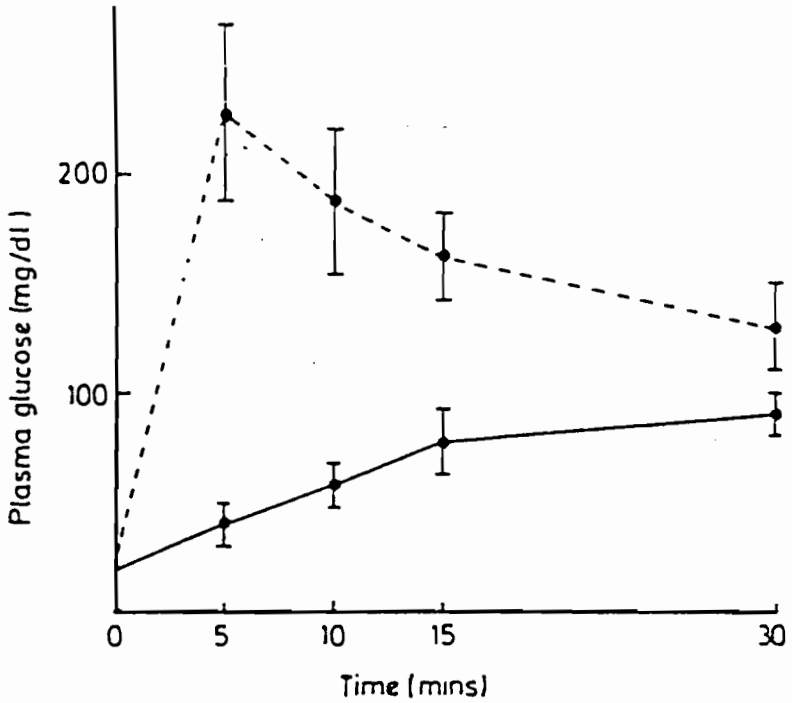

Figure 3 Intravenous injection of glucagon (1 mg) and D50 (25 g). Glycaemic profiles after glucagon (solid line) and dextrose (dashed line) expressed as means with 95% confidence limit (32).

intravenous dextrose group was significantly less than that in the glucagon group, the median time difference (6 minutes) was small in comparison with the total duration of hypoglycaemic coma (120 minutes in both groups). It is clear that the fact that two patients needed supplemental dextrose therapy in the glucagon group was the result of the slower glycaemic response of this agent. The need for 'rescue' therapy was not predictable on the basis of either a clinical history or presenting glucose level, nor did either patient evidence alcohol ingestion or hepatic disease.

III. PREHOSPITAL TREATMENT OF HYPOGLYCAEMIA WITH GLUCAGON

Although the use of intramuscular or subcutaneous glucagon has appeared to have some obvious potential advantages for prehospital care of patients with severe hypoglycaemia, it is only in the last two years that this aspect has been systematically investigated. The great frequency of hypoglycaemic

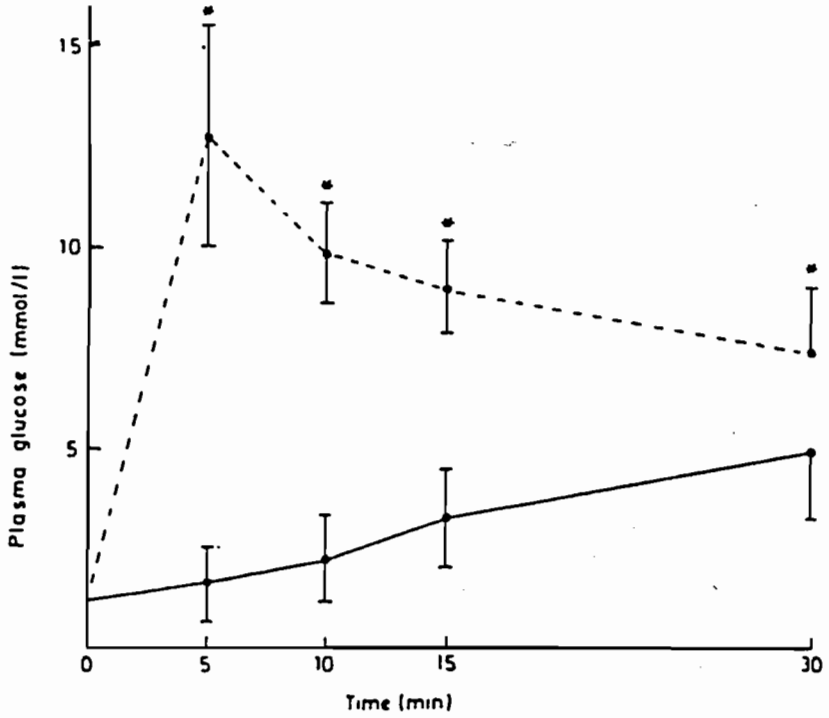

Figure 4 Intramuscular injection of glucagon (1 mg) compared with intravenous injection of D50 (25 g). Glycaemic profiles after glucagon (solid line) and dextrose (dotted line). Significant differences are indicated by asterisk (*). Note similarity to Figure 3[34].

reactions in the general outpatient diabetic population has already been noted[32,33] and the prehospital 'diagnosis' of altered consciousness is even more common. Paramedical personnel in Europe and the United States are increasingly able to administer intravenous therapy. However, several concerns, including an unnecessary increase in on-scene time and the expense and morbidity of unnecessary intravenous therapy, make the possibility of non-intravenous therapy an attractive alternative.

Vukmir *et al.* reported on 50 consecutive prehospital patients presenting with hypoglycaemia (documented by Chemstrip analysis of less than 80 mg/dl) and symptoms of decreased consciousness, syncope or seizures[35]. In this prospective non-randomized trial, patients were eligible for infusion only if an intravenous access could not be obtained by a paramedic in three attempts, a ten minute time limit, or there was a clinical impression of inadequate venous access. All patients were administered a 1.0 mg dose of glucagon (0.5 mg for children) subcutaneously or intramuscularly. Measured endpoints

Table 1. Improvement in serum glucose and mental status after prehospital treatment with subcutaneous or intramuscular glucagon. 'Qualitative' refers to assessment on 0–3 scale; quantitative is Glasgow Coma Scale scoring[5].

	Pretreatment	*Post-treatment*
Glucose (mg/dl)	33.2 ± 23.3*	133.3 ± 57.3*
Mental Status		
Qualitative	1.26 ± 0.96*	2.42 ± 0.94*
Quantitative	9.00 ± 4.19*	13.04 ± 3.68*

*$p < 0.001$

were (a) post-treatment glucose (determined by serum analysis at the receiving hospital), (b) pre-treatment and post-treatment level of consciousness scores assessed on a qualitative linear scale ranging from 0 to 3 (with 0 being unresponsive and 3 being completely alert), and (c) estimate of the Glasgow Coma Score in the usual fashion. Fifty-four percent of the patients (27 of 50) had Chemstrips of less than 40 mg/dl and 80% (40 of 50) had conditions such as diabetes mellitus, alcohol abuse or chronic renal failure that would make them at risk for hypoglycaemia. Twenty-nine of the 50 patients (58%) were insulin dependent. The route of glucagon administration was arbitrary, listed as intramuscular in 46 of the 50 and subcutaneous in the remaining four.

The results of Vukmir *et al.*'s study indicated that the therapeutic intervention resulted in a mean increase in measured glucose of 100.1 mg/dl ($p < 0.001$). Improvement in mental status as well as serum glucose level was noted with the level of consciousness scores increasing by 1.16 on the qualitative scale and Glasgow Coma Scores increasing from 9.0 to 13.04 on the quantitative scale ($p < 0.001$) (Table 1). The mean time for this effect to be noted was 8.85 ± 4.37 minutes in those patients who responded on both scales (41 of 50, 82%). Analysed according to final diagnosis as obtained from in-patient hospital records, 35 of the 50 (70%) had a primary diagnosis of hypoglycaemia. This group, referred to as 'responders', had an increase of 1.4 on the qualitative scale and 5.7 on the quantitative mental status assessment (Table 2). The second group of patients (15 of 50, 30%) were those diagnosed with a secondary diagnosis of hypoglycaemia who had other abnormalities also responsible for the altered mental status including cerebrovascular accident, sepsis and malignancy. This 'non-responder' group was clearly differentiated by a small and insignificant change of 0.40 on the qualitative scale and 0.20 on the quantitative scale of mental assessment. However, glucose level in this group also increased with glucagon therapy.

Vukmir *et al.* noted that their prehospital population at risk for hypoglycaemia was likely to have difficult intravenous access and therefore they were likely candidates for glucagon therapy. Included were those with drug use

Table 2. Analysis by hospital diagnosis of glucagon effect. Note that patients with eventual primary diagnosis of hypoglycaemia (responders) had a much greater response to glucagon than did the group with other diagnoses (non-responders)[35].

	Pretreatment	*Post-treatment*
Responders (70%, 35/50)		
Qualitative	1.28 ± 0.98*	2.68 ± 0.50
Quantitative	8.48 ± 3.98*	14.05 ± 2.36
Nonresponders (30%, 15/50)		
Qualitative	1.33 ± 1.04	1.73 ± 1.27
Quantitative	10.13 ± 4.50	10.33 ± 4.50

*$p < 0.0001$

(11.1%), alcohol abuse (14.8%) and chronic renal failure and congestive heart failure (16.6%), in addition to those with diabetes mellitus. It was hypothesized that the patient with acute and chronic alcohol abuse might not respond to glucagon. However, none of the 7 patients with known alcohol abuse were refractory to glucagon. Reported side effects in this series were rare with only a single case of headache noted. The drug was administered to one pregnant patient. The authors found no absolute contraindications to the use of glucagon, clearly an advantage in the prehospital setting. Furthermore, the degree of glycaemic rise noted in the study was similar to that achieved in experimental work with normal subjects. The authors concluded that glucagon is a safe and effective prehospital therapy for hypoglycaemia in cases where intravenous line access is difficult.

The only other reports of glucagon use in the prehospital sector emanate from the United Kingdom. Yaxley *et al.*[36] and Steel *et al.*[21] reported favourable results with subcutaneous glucagon given by ambulance personnel when oral therapy was impossible or unsuccessful. In Steel *et al.*'s uncontrolled study, 76 of 103 patients received glucagon. Twenty-four patients refused to be transported to the hospital upon recovery, and an additional 62 were discharged from the emergency department after either no treatment or simple oral re-feeding. Only 10 were given intravenous glucose and none were admitted to the hospital for treatment of hypoglycaemia. In the absence of a control group it was not possible to state what effect prehospital administration of glucagon might have had. Comparison with a retrospective series representing a similar 7 month period prior to glucagon institution revealed that 50 patients required intravenous glucose at that time as opposed to 10 in the current series. According to the authors, the prehospital administration of glucagon has extended to all of Scotland and there is evidence that glucagon is being used in the prehospital phase in many other areas as well.

IV. SPECIAL CONSIDERATIONS IN THE EMERGENCY USE OF GLUCAGON FOR SEVERE HYPOGLYCAEMIA

Although the use of glucagon for severe hypoglycaemia is usually straightforward, there are special situations where particular considerations apply.

Sulphonylurea induced hypoglycaemia

Since the mid-60s, there has been an ongoing discussion as to the advisability of glucagon use in cases where hypoglycaemia is caused by oral hypoglycaemic agents of the sulphonylurea class. This concern is due to two factors: glucagon in experimental models stimulates insulin release; and patients with the protracted hypoglycaemic state sometimes seen with the oral agents might have a very depleted or no storage of hepatic glycogen, thereby minimizing the effects of glucagon. Davies[20] argued in favour of the use of glucagon together with glucose for patients with sulphonylurea induced hypoglycaemia and presented a case in support of this regimen. Marri *et al.*[37], amongst others, maintain that glucagon should never be used in sulphonylurea cases, and presented a patient with chlorpropamide and phenformin overdosage who 'showed signs of collapse' shortly after receiving glucagon therapy. In both normal and diabetic subjects, before and during treatment with chlorpropamide, blood sugar concentrations reliably increased when given glucagon through the intramuscular or intravenous route. The authors noted that hypoglycaemia does not seem to be provoked. Currently it is suggested that glucagon be administered for sulphonylurea induced hypoglycaemia just as with other causes. Recent clinical studies have routinely included such patients without observing a different response.

Acute and chronic alcoholism

Hypoglycaemia has been associated with both acute and chronic alcoholism through several mechanisms[23,25]. It has been postulated that the glycogen depletion often noted in severe alcoholics minimizes or abolishes the response to glucagon as this response is partially related to glycogenolysis[5,9]. Also, acute and chronic alcoholism interfere with maintenance of normoglycaemia through interruption of gluconeogenesis. This too may be a mechanism by which glucagon normally raises the blood sugar. Unfortunately, there is no clinical study that clearly addresses this issue. Recent clinical series frequently have included a minority of patients that are identified as either acutely or chronically alcoholic but no differences in their response to therapy have been described[32,35,36]. This suggests that glucagon can give an initial glycaemic response even in the patient with alcoholic liver disease; prudence would

dictate that oral replacement of carbohydrates is then rational to maintain such a response.

Neonatal hypoglycaemia

A somewhat similar controversy has arisen in the treatment of neonatal hypoglycaemia. Some reports indicate that neonatal hypoglycaemia is associated with depletion of glycogen stores while others have disputed any such association[12]. The aetiology is no doubt complex and variable. Direct supplementation of glucose, rather than glucagon therapy alone, remains the standard in neonatal disease.

Home administration and intranasal use

For treatment of severe hypoglycaemia to be maximally effective and cost effective glucagon should be utilized as early as possible, prior even to the arrival of paramedical personnel. Glucagon can be administered at home by intramuscular or subcutaneous injection and has achieved a certain degree of popularity in the United Kingdom where approximately 50% of diabetic patients are aware of home use of glucagon[38]. In view of the frequency of severe hypoglycaemic episodes there is no apparent reason why further efforts along these lines should not be pursued. Perhaps with greater potential utility are reports indicating that glucagon, when given by the intranasal route, increases blood glucose both in healthy volunteers and in insulin dependent hypoglycaemic subjects[39,40]. Intranasal glucagon appears to rapidly enter the blood stream and the kinetics closely resemble those of intravenous administration. In hypoglycaemic patients, plasma glucose increases by approximately 100%, peaking at 26 minutes after administration of 7.5 mg of the intranasal drug, and symptoms are relieved in approximately 7 minutes (Figure 5)[40]. Bioavailability of the intranasal form appears to be approximately 10% of that achieved with the parenteral route, on the basis of serum glucose levels. The feasibility of family members administering intranasal glucagon to even comatose patients merits further study.

CONCLUSION

The investigation of glucagon as a treatment for acute hypoglycaemia can be divided into several fairly well-defined stages. Studies in the 60s and 70s established that glucagon is effective in most cases of hypoglycaemia, particularly when caused by insulin excess, and that this effect is relatively independent of age or sex. The minimal dose was not established, but the lack of advantage in using more than 1 mg of glucagon was demonstrated.

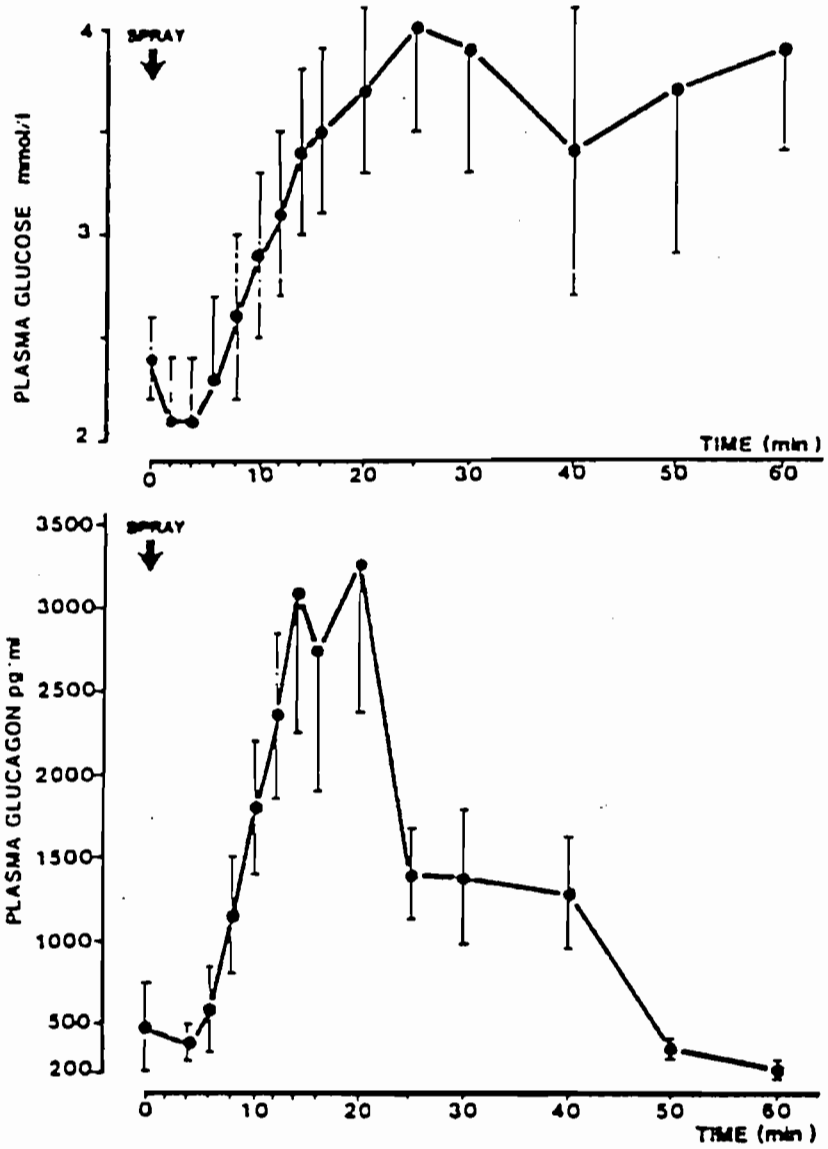

Figure 5 Intranasal administration. Plasma glucose levels and plasma glucagon levels in hypoglycaemic insulin-dependent diabetics after intranasal glucagon[40].

In the late 80s clinical studies appeared that compared glucagon in its various parenteral routes to the more standard dextrose therapy. These latter studies clearly established that (a) the subcutaneous and intramuscular routes were

as effective, although slightly slower in action, than the intravenous one; (b) glucagon could be used as initial therapy by family members; and, (c) when administered parenterally, subsequent intravenous therapy with dextrose was often obviated. Studies in the very early 90s have emphasized the prehospital phase. In both the United States and the United Kingdom studies indicate that glucagon is a safe and effective therapy and can be administered by paramedical personnel. It has particular application in those situations where establishment of an intravenous line is likely to cause significant delay. Future studies will likely center on glucagon administration via novel routes such as the intranasal, and the applicability of glucagon use in specialized hypoglycaemic conditions.

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DISCUSSION

Lefèbvre There has been a recent publication by Chuang *et al.* (Acta Pharm Sinica. 1992;13:193–7) showing that a very significant increase in blood glucose can be achieved by giving glucagon in eye drops. It is very likely that giving a couple of drops in each eye of the diabetic child can be easier for parents than giving an injection. One can get a very good increase in both glucagon and glucose.

Heller Did they measure the dose?

Lefèbvre Yes, I think it is below 1 mg. This is again something that we can discuss right now. Probably even 1 mg, from a metabolic point of view, is much more than what is needed. What we do is to give most people half a milligram.

Zaloga We give the families a milligram vial of glucagon to take home, even for kids. If it is for kids, the parents frequently do the insulin injections anyway, and injecting glucagon or insulin is the same. The spouses are instructed on how to give both glucagon and insulin. We usually teach one of the care-providers living with the patient to inject the insulin or glucagon. They do not express particular problems with it. So, I am not so sure that there is a dire need to look for all kinds of other extraneous routes of administration when, in fact, people who have needles and syringes, or pre-filled syringes, can easily do the injections, subcutaneously or intramuscularly. Even if they get it into the vein it does not matter.

Heller Do you really think so?. The reason I hesitate is because in that series reported by Mühlhauser *et al.* in 1985 the patients were adults, yet in approximately 30% of instances where glucagon was available in the home, there was a hypoglycaemic episode in which the ambulance was called and people were transferred rather than administered glucagon. This clinic sounds like a good one, where they did diabetic training of the families as part of the study. They had a whole list of reasons why glucagon was not given, with anxiety being number one, concern about the diagnosis being number two, forgot about it number three, etc... I do think that with a little more education and training certainly this problem could be overcome.

Zaloga My guess is that if they are concerned about giving it by injection, they are going to forget the eye drops and all the other strange routes as well.

Ros Did the studies find that hypoglycaemic neonates do not respond to glucagon?

Heller Yes, from my reading of the literature there is debate over the question of glycogen stores being very depleted (Landunne MA. Arch Dis

Child. 1972;47:754–9). There seems to be concern about relying on glucagon to the exclusion of intravenous glucose; glucagon probably raises blood sugar in these children, but it should not be relied on to the point of excluding the use of glucose.

Ros Do you recall whether anybody actually measured endogenous glucagon levels?

Lefèbvre Yes, my colleagues Massi-Bénedetti and Luyckx measured glucagon in the portal blood of healthy neonates, premature babies and infants of diabetic mothers. All of them had endogenous glucagon (Luyckx A, Massi-Bénedetti F, Falorni A, Lefèbvre PJ. Diabetologia. 1972;8:296–300). This indicates that glucagon is one of the very crucial hormones for the adaptation to extrauterine life. Very, very few cases of hypoglycaemia in neonates are due to a real glucagon deficiency. Some of these cases are due to β-cell hyperplasia, therefore glucagon will be harmful because of massive insulin release. Hypoglycaemia is due also to a variety of congenital diseases, inborn errors of metabolism, and there the glucagon test is used as a diagnostic tool. For instance, in the various forms of glycogenosis, the response to glucagon is useful for diagnosis. I think that in type-I you have no response, due to abnormality in the glucose-6-phosphatase. I would say that one has to be very cautious in using glucagon in hypoglycaemia of neonates.

GLUCAGON

in acute medicine

Edited by
J. Picazo MD

About the Book

As a reflection of the growing interest in this field, an International Workshop on Glucagon in Acute Medicine was held in Barcelona in October 1992. This book of proceedings of the Workshop provides up-to-date, relevant information on the use of glucagon, a gastrointestinal hormone produced in the pancreatic α-cells, in different clinical emergencies.

Recent findings on the use of glucagon are reviewed by a group of experts from different fields of medicine (cardiology, internal medicine, endocrinology, diabetology, clinical toxicology, surgery, paediatrics, gastroenterology, hepatology, radiology). The data offered covers a wide range of situations within acute medicine and should be of use to physicians, researchers and emergency workers in their daily professional lives. The stimulating discussion that follows each presentation should inspire professionals interested in emergency and critical care medicine to continue research on, as well as explore new uses of, this gastrointestinal hormone.

The recent research findings and discussion on the use of glucagon in emergency medical situations, presented here, add a new and fascinating facet to the growing literature on the importance of acute medicine. This volume is the fourth on a series of Workshops on glucagon (*Glucagon In Gastroenterology*, MTP Press, 1979; *Glucagon in Gastroenterology and Hepatology*, MTP Press, 1982; *Glucagon In 1987*, MTP Press/Kluwer, 1987).

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