

Retrospective evaluation of the use of glucagon infusion as adjunctive therapy for hypoglycemia in dogs: 9 cases (2005–2014)

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Abstract

Objective – To describe the use of glucagon infusion for adjunctive treatment of hypoglycemia in dogs.

Design – Multicenter retrospective case series.

Setting – One university and 1 private veterinary referral hospital.

Animals – Dogs were included if they were hospitalized and received glucagon therapy for hypoglycemia, defined as blood glucose concentration (BG) <60 mg/dL. A total of 9 dogs were included from September 2005 to May 2014.

Interventions – None.

Measurements and Main Results – The medical record for each eligible case was reviewed. Data recorded included signalment, presenting complaint, underlying disease process, presenting BG, BG after dextrose supplementation, BG before glucagon administration, maximum BG while receiving glucagon, and BG after discontinuation of glucagon, if available. Adverse reactions to glucagon and outcome of case were recorded if available. The most common causative disease was insulinoma ($n = 7$). Median serum glucose concentration on presentation was 30 mg/dL (20–41 mg/dL). The median bolus of glucagon was 50 ng/kg followed by a median maximum dose of a glucagon CRI of 15 ng/kg/min. The mean time period on glucagon CRI until normoglycemia (defined as BG > 60 mg/dL) was 7 hours. All hypoglycemic patients had improvement of BGs when glucagon was added. Statistically significant differences ($P < 0.05$) were found between BG measurements on glucagon CRI compared to BG at presentation, BG after dextrose, and BG prior to glucagon with a Friedman statistic of 17.3. A CRI was found to effectively increase the BG without recurrence of hypoglycemia after weaning. The majority of patients (5/9) survived to discharge.

Conclusion – Glucagon CRI was accompanied by an increase in BG in hypoglycemic dogs. Glucagon CRI appears to be a safe method and can be readily utilized in most practice settings.

(*J Vet Emerg Crit Care* 2016; 26(6): 775–781) doi: 10.1111/vec.12513

Keywords: canine, dextrose, hypoglycemic, insulinoma

Abbreviations

BG blood glucose concentration
CRI constant rate infusion

Introduction

Hypoglycemia is defined as blood glucose concentration (BG) < 3.3 mmol/L [60 mg/dL].¹ It may result in a variety of clinical signs and can be caused by multiple diseases.¹ The clinical manifestations and severity depend on the degree of hypoglycemia, rate of BG decline, and duration of hypoglycemia.¹ The clinical signs of hypoglycemia, such as altered mentation, weakness, ataxia, or seizures, are most commonly attributed to neuroglycopenia since neurons depend on a concentration gradient for intracellular glucose transport.² Other documented clinical signs include vomiting, anorexia, diarrhea, pacing, and cardiovascular collapse.^{2,3}

While treatment of the underlying disease process is ultimately required, symptomatic treatment of the hypoglycemia is often required while awaiting a diagnosis.

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The authors declare no conflicts of interest.

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Submitted September 20, 2014; Accepted February 26, 2015.

Initial treatment consists of intravenous dextrose as bolus therapy followed by a constant rate infusion (CRI) if hypoglycemia persists.¹ The standard dosing is a 0.5–1 g/kg bolus followed by a CRI with dextrose concentration ranging from 1.25% to 10% in crystalloid fluid.⁴ However, cases exist in which hypoglycemia does not resolve with dextrose administration alone or in which large doses of dextrose are contraindicated. Patients suffering from a functional beta cell tumor (commonly and hereafter referred to as insulinoma) may have exacerbation of clinical signs caused by rebound hypoglycemia. Rebound hypoglycemia occurs when dextrose administration leads to marked insulin release from pancreatic beta cells, which causes acute recurrence of hypoglycemia.⁵ In such cases, different therapeutic strategies should be instituted.

Glucagon has been used to treat hypoglycemia in people,^{6,7} and such use has been described in a single case report in veterinary medicine.⁸ A study evaluating the use of glucagon and its effect on BG in healthy human volunteers demonstrated that intravenous glucagon significantly increased BG.⁹ Although this study demonstrated efficacy regarding glucagon's ability to increase BG, there is a paucity of clinical evidence to support its use in treatment of hypoglycemia in veterinary patients.

This descriptive retrospective study aims to report clinical cases of hypoglycemia managed with glucagon CRI, describing clinical signs, concomitant diseases, protocols used, glucagon CRI impact on BG, adverse effects of glucagon, and final outcome.

Materials and Methods

Cases

The electronic database of the Ohio State University Veterinary Medical Center and Capital Veterinary Referral and Emergency Center (Hilliard, OH) was searched for canine patients diagnosed with hypoglycemia (defined as BG < 3.3 mmol/L [< 60 mg/dL]) between September 2005 and May 2014. Inclusion criteria were hospitalization and glucagon therapy as treatment for hypoglycemia. Medical records were reviewed and the following data recorded: signalment; presenting complaint; disease process confirmed or presumed to be causing hypoglycemia; BG at presentation, after dextrose^a administration, before glucagon^{b,c} administration, maximum while receiving glucagon, and after discontinuation of glucagon; and clinical outcome.

Data collection

Whole BG measurements were obtained by point-of-care glucometer^d or blood gas analyzer.^e For all data points with BG recorded as < 1.1 mmol/L [20 mg/dL] (lower

limit of detection for the assays used), the value used for calculations was 20 mg/dL to allow for standardization for data analyses. For all time calculations, values were estimated to nearest hour.

Statistical analysis

Descriptive statistics were calculated for all clinical and laboratory variables. Data were analyzed for normality with commercial software^f through visual graphical assessment and normality testing with Kolmogorov–Smirnov. Normally distributed data were presented as mean (\pm standard deviation). Data not normally distributed were presented as median (range). For consistency, the BG data were described as median (range). To evaluate for statistical significance between the BG values at specified time points, a nonparametric test for multiple samples was performed using the Friedman test. Only those subjects with a complete data set were statistically evaluated. A Student's *t*-test was performed to compare time to euglycemia between those subjects that received an initial glucagon bolus and those that did not receive a glucagon bolus. $P < 0.05$ was considered statistically significant.

Results

Nine dogs were included in the study. Five cases were included from The Ohio State University and 4 cases from Capital Veterinary Emergency and Referral Center. The cases consisted of spayed females ($n = 4$), castrated males ($n = 4$), and 1 intact male. Mean age was 9.2 ± 2.9 years. Breeds represented included mixed breed ($n = 3$), with a single case each of Golden Retriever, French Bulldog, Beagle, Jack Russell Terrier, Bichon Frise, and Boxer.

The most common presenting complaint was seizure ($n = 7$), and a single presentation each for vomiting and agitation. Most patients had acute onset of clinical signs, although some patients had previously documented episodes of hypoglycemia ($n = 4$) or previously documented neurological signs ($n = 5$). Four patients had been previously diagnosed with insulinoma via insulin:glucose ratio; 3 were being managed with corticosteroids. Another 2 patients were being treated with subcutaneous insulin for diabetes mellitus. One of the diabetic patients had also been previously diagnosed with an adrenal tumor invading the caudal vena cava and renal vein, a grade 1 soft tissue sarcoma, hypothyroidism, keratoconjunctivitis sicca, and cataracts. This patient had been receiving insulin, diclofenac 0.1% solution, and cyclosporine ocular suspension. Another patient had been diagnosed with heart disease (further description is

unknown) and was receiving furosemide and enalapril. Two patients had no pertinent previous medical history.

Presenting physical examination findings included neurological abnormalities ($n = 9$) ranging from dull mentation to seizure activity. Other physical examination findings included hypothermia ($n = 3$), tachycardia ($n = 1$), heart murmur ($n = 1$), bradycardia ($n = 1$), and weakness ($n = 1$). The most common diagnostic tests performed at admission were BG ($n = 9$), CBC ($n = 6$), and serum biochemistry profile ($n = 6$). One patient also had a paired fasting insulin:glucose ratio performed. For the patients with hematocrit recorded ($n = 6$), 1 was mildly anemic with a hematocrit of 31% (reference interval, 36–54%). Additional diagnostic testing performed and treatment administered were done at the clinician's discretion. Therapy other than dextrose or glucagon during hospitalization varied with the most common being steroid administration ($n = 5$), benzodiazepines ($n = 3$), mannitol ($n = 3$), and ondansetron ($n = 3$).

Insulinoma was found to be the most common underlying cause for hypoglycemia in these patients ($n = 7$, 78%), with 4 having been previously diagnosed. Of the 3 not previously diagnosed, diagnosis was made via insulin:glucose ratio, surgical histopathology, or postmortem histopathology ($n = 1$ for each). The final dog had been previously diagnosed with diabetes mellitus and was receiving insulin therapy at the time of the episode. While insulin overdose was considered a possible cause for hypoglycemia, it was determined to be unlikely given that the owner was a veterinarian, the last insulin dose had been administered >12 hours prior to presentation, and an insulinoma was found on postmortem histopathology. One of the 2 patients without diagnosis of insulinoma was diagnosed with atypical hypoadrenocorticism based on an ACTH stimulation test, though it was also receiving insulin therapy for previously diagnosed diabetes mellitus. The final dog without diagnosis of insulinoma had no definitive diagnosis, as further diagnostics were declined.

The median presenting BG was 1.7 mmol/L [30 mg/dL] (1.1–2.3 mmol/L [20–41 mg/dL]). All patients received a bolus of dextrose at presentation, with a mean dose of 0.7 g/kg (± 0.5 g/kg). The median BG after dextrose bolus was 2.8 mmol/L [50.5 mg/dL] (1.1–4.3 mmol/L [20–78 mg/dL]). Eight patients received a CRI of dextrose with a mean maximum concentration of 6.4% ($\pm 4.7\%$), and the timing of dextrose supplementation and glucagon administration varied. However, all 8 patients continued to receive dextrose as a CRI after initiation of glucagon therapy. The median BG prior to glucagon administration was 1.4 mmol/L [25 mg/dL] (< 1.1–3.4 mmol/L [20–61 mg/dL]). The median length of time after presentation until glucagon

administration was 4 hours (1–45 h). When a loading glucagon bolus was administered ($n = 6$), the median dose was 50 ng/kg (15–50 ng/kg). The CRI dose varied with a median maximum rate of infusion of 15 ng/kg/min (9–50 ng/kg/min). The mean length of time on glucagon CRI until normoglycemia (defined as blood glucose ≥ 3.3 mmol/L [60 mg/dL]) was 7 hours (± 4.4 h). The median highest recorded BG while receiving glucagon was 8.1 mmol/L [146 mg/dL] (4.3–11.6 mmol/L [77–209 mg/dL]). The mean total length of time on a glucagon CRI was 18.1 hours (± 10.6 h), and the median BG at discontinuation of the glucagon was 4.9 mmol/L [89 mg/dL] (3.9–6.5 mmol/L [70–117 mg/dL]). There was a statistically significant difference ($P < 0.05$) between BG at all other time points compared to maximum BG on glucagon, with a Friedman statistic of 17.3 (Figure 1). All patients experienced increases of BG while on glucagon compared to measurements obtained before glucagon administration (Figure 2). Within the present population, calculation of mean time to euglycemia was 4.8 ± 2.4 hours for those patients that received an initial glucagon bolus compared to 10.7 ± 4.9 hours for those patients that did not receive a bolus. However, comparison of these groups approached but did not achieve statistical significance ($P = 0.1$). The majority of dogs ($n = 6$) had gradual increases in BG while receiving the glucagon CRI; once normoglycemia was established, the majority ($n = 7$) maintained euglycemia. One patient was documented to have abrupt changes in BG, and was also the only dog that could not be successfully weaned from glucagon infusion. However, this patient was normoglycemic prior to euthanasia.

Once normoglycemia was documented, glucagon CRI was either continued without adjustment or slightly decreased until the next BG measurement was obtained. Adjustments to CRI dosing were made based on BG measurement and clinician preference. Information on glucagon taper was available for 4 patients. The mean time from persistent normoglycemia until glucagon taper was initiated was 12 ± 7.3 hours. The mean length of time over which the glucagon taper was performed was 9.5 ± 8.5 hours. For a single patient, the glucagon CRI was discontinued without a taper. Of those patients documented to be successfully weaned from the glucagon CRI ($n = 5$), there were no reports of recurrent hypoglycemia. Two patients with insulinoma had recurrence of hypoglycemia in the face of high supplementation rates of both dextrose and glucagon. Both had documentation of BG > 3.3 mmol/L [60 mg/dL] while on glucagon therapy. However, for 1 dog, subsequent BG measurements demonstrated a recurrence of hypoglycemia along with a seizure. The other had recurrence of hypoglycemia after obtaining normoglycemia, but

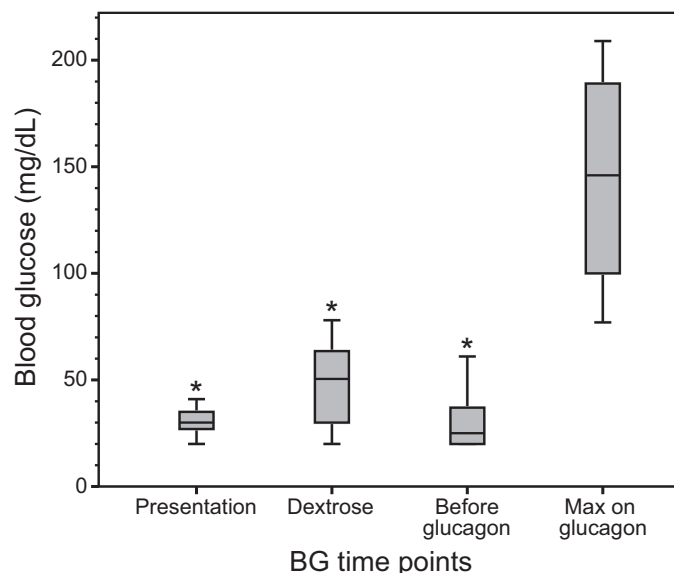


Figure 1: Box and whisker plot demonstrating the median BG measurements with interquartile range comparing measurements taken at 4 time points. BG, blood glucose concentration; CRI, constant rate infusion; presentation, BG at presentation; dextrose, BG after dextrose bolus; before glucagon, BG before glucagon administration; max on glucagon, maximum recorded BG while receiving glucagon CRI. * $P < 0.05$ compared to maximum BG receiving glucagon CRI.

the last documented BG was 5.6 mmol/L [100 mg/dL]. Neither patient was successfully weaned from glucagon therapy.

Some of the patients in this study were concurrently receiving steroids. Three of the patients previously diagnosed with an insulinoma were receiving oral steroids (prednisone or prednisolone) at the time of presentation. However, these patients were hypoglycemic despite steroid administration; only after glucagon administration was an increase of BG demonstrated and euglycemia obtained. Long-term management for these patients is unknown from the medical records; therefore, persistence of normoglycemia after discharge is unknown. Known additional therapy that may have contributed to normoglycemia at the end of hospitalization and/or after discharge was corticosteroids ($n = 5$), both continued administration of previously prescribed ($n = 3$) or newly begun therapy ($n = 2$), and 1 laparotomy for gross tumor resection.

The only adverse effects attributed to glucagon CRI recorded was mild hyperglycemia (defined as > 11.1 mmol/L [200 mg/dL])¹⁰ in 1 patient, with the highest recorded BG of 11.6 mmol/L [209 mg/dL] prior to taper of the glucagon CRI. The documented hyperglycemia had no attributable clinical signs. Five patients were discharged from the hospital, 3 were euthanized and 1 was transferred to a different veterinarian and lost to follow-up. Of the cases that were euthanized, the recorded reason for euthanasia was poor prognosis ($n = 2$) and poor prognosis with financial constraints ($n = 1$).

Discussion

This case series reports the use of a glucagon CRI as a treatment in the management of hypoglycemia. Although treatment of hypoglycemic patients typically warrants initial stabilization with dextrose supplementation, this report supports the use of glucagon CRI if initial therapy fails or to avoid administration of a high dextrose concentration.

Glucagon is a 29-amino acid polypeptide hormone secreted from the pancreatic α cells. Its primary function is to maintain glucose production via glycogenolysis and gluconeogenesis principally in the liver.^{9,11} Glucagon has a highly conserved amino acid sequence, making both recombinant and animal source glucagon viable options as treatment for hypoglycemia.⁹

Although glucagon has been recommended for treatment of hypoglycemia in both people and animals,^{1,6,7,12} there is only 1 canine case report⁸ and limited studies in healthy small animals.^{11,13} One study evaluated the effects of longer term administration of glucagon in healthy dogs and cats using several concentrations of glucagon, ranging from 0.4 to 18 mg/24 hours, with various routes of administration including intramuscular, intravascular, and intraperitoneal.¹³ The duration of glucagon administration varied from 5 to 108 days. These animals experienced hyperglycemia for 1–3 hours following each single glucagon injection, and sustained hyperglycemia if receiving a CRI. All animals returned to baseline serum glucose concentrations following

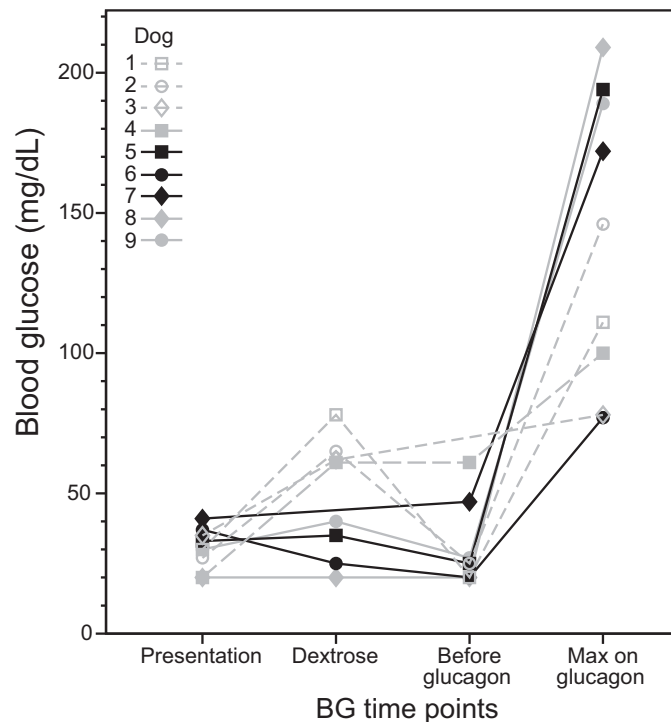


Figure 2: Line graph depicting BG measurements at 4 time points for dogs receiving glucagon for hypoglycemia. BG, blood glucose concentration; presentation, BG at presentation; dextrose, BG after dextrose bolus; before glucagon, BG before glucagon administration; max on glucagon, maximum recorded BG while receiving glucagon.

discontinuation of the glucagon, and there were no toxic effects, weight loss, or prolonged hyperglycemia noted with long-term administration of glucagon.¹³ A more recent study comparing glucagon administration by subcutaneous and intravenous injection found significant increases in glucose concentrations 10, 20, and 30 minutes following administration.¹¹ Significantly higher BG values were noted following intravenous administration compared to subcutaneous.¹¹ This finding is consistent with data from healthy human volunteers, in whom the time to maximum BG was shorter after intravenous glucagon administration compared to intramuscular and subcutaneous routes.⁹

Based upon pharmacokinetic data, it is recommended that glucagon be administered as a CRI rather than intermittent injection, because time to peak plasma concentration is approximately 20 minutes in dogs.¹¹ In the cases reported here, some patients received an initial loading bolus of glucagon. Variable doses and dosing adjustments were attributed to clinician preference and patient need; those cases with more severe hypoglycemia or clinical signs were more likely to receive a higher initial bolus dose. Although a statistically significant difference regarding time to euglycemia was not found between dogs receiving a bolus and those not receiving a bolus, this study is likely underpowered

to detect such difference. Statistically significant differences were found when comparing all time points to the maximum BG on glucagon, supporting the notion that glucagon aided in increasing these patients' BGs. Given the short half-life of glucagon, it is generally recommended to gradually taper the glucagon CRI. Five patients in this study were weaned from glucagon by gradual taper, though the time length varied between patients. Though it is impossible to determine given the retrospective nature of this study, it is presumed that BG stabilization and resolution of the clinical signs were the triggers used to initiate tapering. The majority of patients ($n = 6$) experienced a gradual BG elevation when glucagon therapy was initiated. However, given the variable timing of BG measurements, the true BG fluctuations while receiving continuous glucagon infusion are unknown. In order to better document the response to glucagon CRI, more frequent or continuous BG measurement may be of benefit in future studies.

Many conditions may result in hypoglycemia in small animals. These include iatrogenic insulin overdose, insulinoma, xylitol toxicosis, hypoadrenocorticism, sepsis, and paraneoplastic disease.^{2,5,14–19} Two of the patients in this series were receiving exogenous insulin for previously diagnosed diabetes mellitus; 1 was then diagnosed with hypoadrenocorticism and 1 with

an insulinoma. Although the timing of prior insulin administration could not be determined from the medical records in either case, it is possible that concurrent exogenous insulin overdose may have contributed to the clinical hypoglycemia, making the hypoglycemia multifactorial. Regardless, it has been shown that following insulin overdose, the BG may continue to decrease after admission as the insulin continues to be systemically absorbed.²⁰ While many patients suffering from hypoglycemia secondary to insulin overdose respond well to dextrose supplementation, the addition of glucagon can be considered for those patients with persistent hypoglycemia despite standard therapy. One of the diabetic patients was remarkable, given the diagnosis of an insulinoma in a diabetic dog. Only 1 other such case has been published in the veterinary literature²¹; concurrent diabetes mellitus and insulinoma is also a very rare occurrence in human medicine, with only case reports available.^{22–32} Although uncommon, the possibility of a concurrent insulinoma should be considered when a diabetic patient suspected of having an insulin overdose fails to respond to initial glucose supplementation.

The population described here experienced hypoglycemia that did not have an immediate response to dextrose supplementation. The majority of the cases were diagnosed with insulinoma. Although diagnosis of insulinoma is controversial, current methods include histopathological evidence of a neuroendocrine tumor or demonstration of hyperinsulinemia with concurrent hypoglycemia in the face of clinical signs.^{5,16} Of the patients in this series with insulinoma, the majority ($n = 5$, 71.4%) were diagnosed using an insulin:glucose ratio, which was performed at different laboratories. It is commonly accepted that an insulin:glucose >30 , with appropriate clinical signs, is considered diagnostic of insulinoma.⁵ Dextrose administration may exacerbate insulin release from an insulin-secreting tumor, which can cause rebound hypoglycemia.¹ For this reason, it is possible that concern for insulinoma may have resulted in subtherapeutic administration of dextrose bolus therapy. Two dogs with insulinoma had persistent hypoglycemia and could not be weaned from glucagon. Although it is possible that additional time on a glucagon CRI may have improved these patients' clinical condition and BGs, the owners of both dogs elected humane euthanasia based on prognosis. The majority of dogs ($n = 7$, 78%) had good clinical resolution of hypoglycemia and clinical signs.

As previously mentioned, there were several patients that either were receiving corticosteroids prior to admission or were discharged with corticosteroids. Although time of steroid administration in relation to BG measurements could not be made, many patients in this series did not experience improvement in BG measurements until

glucagon was administered. Such is true for 1 patient that did not achieve normoglycemia until approximately 16 hours after receiving an injectable corticosteroid, but was also receiving glucagon. A second patient received dexamethasone 2 hours after presentation and shortly after starting glucagon. This patient became euglycemic 5 hours later. Given the administration of several therapies, it is difficult to discern which may be responsible for the BG increase. Glucocorticoids antagonize insulin at the cellular level and stimulate hepatic glycogenolysis. As such, their effects are not expected to be immediate.³³ While corticosteroids may have affected these patients' BGs, there is temporal association that suggests that the glucagon CRI was beneficial.

Given the retrospective and multicenter nature of this case series, there are several limitations. Retrospective evaluation of the medical records revealed some incomplete data sets and loss of case material, which can lead to selection bias. Also, these cases were not matched to a control population. Another limitation is that many different point-of-care instruments were used for initial and serial BG measurements. This may have caused some inpatient and interpatient variability in results. Future studies should consider standardizing the use of a single validated and calibrated instrument when measuring BG. Given that the majority of patients within this population were diagnosed with or presumed to have an insulinoma, glucagon may have been administered earlier than it would have been in other case types, which may have biased the findings. However, while it is possible that these patients may have responded to dextrose alone, glucagon administration may have led to faster resolution of hypoglycemia. Future prospective studies will be needed to determine whether glucagon administration in the insulinoma patient allows faster resolution of clinical signs compared to dextrose alone. Future studies may consider the delay of corticosteroid administration in insulinoma patients to remove their influence. Additionally, the length of time between dextrose or glucagon administration and BG measurement was impossible to determine in most cases. Therefore, the length of time between BG measurement and therapy adjustment is unknown. An additional limitation is the lack of a documented hematocrit for all patients in this series. It has been documented that hematocrit affects BG measurement, with a positive bias in anemic patients and a negative bias with increased hematocrit.³⁴ It is therefore possible that patient hematocrit may have affected BG in the patients without a recorded hematocrit. A final limitation was the variety of clinicians managing a small number of cases. This may have influenced the time to initiation of glucagon, whether or not to administer a bolus dose, the dose of any glucagon bolus, adjustment of glucagon CRI, determination of the time for

discontinuing the glucagon CRI, and other supportive therapies. This study supports the need for a future prospective study to determine which disease processes may benefit from glucagon therapy, the potential benefit of bolus administration followed by CRI, and the optimum dose of glucagon.

The findings of this study support the use of a glucagon CRI as a feasible adjunctive therapy to dextrose therapy for the treatment of refractory hypoglycemia. Although dextrose treatment will continue to be the mainstay of supportive care, glucagon may be considered in cases of insulinoma or those cases with limited response to dextrose alone.

Footnotes

- ^a Dextrose solution 50%, Butler Schein™ Animal Health, Dublin, OH.
^b GlucaGen® glucagon (rDNA origin) for injection, Bedford Laboratories™, Bedford, OH.
^c Glucagon 1mg Emergency kit rDNA, Lilly, Indianapolis, IN.
^d Accu-check® glucometer, Roche Diagnostics, Indianapolis, IN.
^e NOVA Critical Care Xpress®, Nova Biomedical, Waltham, MA.
^f IBM SPSS Statistics, IBM, Armonk, NY.

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