The use of hyperinsulinemia-euglycemia therapy in the treatment of amlodipine overdose in a dog.

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Key Clinical Message: Hyperinsulinemia-euglycemia therapy (HIET) can be used for treatment of hypotension as well as other clinical signs associated with calcium channel blocker toxicosis. The use of HIET should be considered for amlodipine toxicosis in dogs.

Introduction

Amlodipine is a frequently prescribed drug used to control hypertension in human and small animal patients[1]. This dihydropyridine calcium-channel blocker (CCB) inhibits the influx of calcium ion into the cell through the L-type calcium channel, causing peripheral vasodilation and afterload reduction[1]. Amlodipine is metabolized by the liver, widely distributed and highly protein bound, with a long half-life of approximately 30 hours in dogs[2]. While generally well tolerated, reported adverse reactions of amlodipine have been described at doses within the recommended range of 0.1-0.4 mg/kg PO q24[3–5].

The minimum oral toxic dose of each CCB has not been well established in humans or animals, but signs of toxicity have been reported in CCBs at therapeutic doses[6]. Toxic doses of CCBs have been associated with significant morbidity and mortality[6]. Clinical signs in affected animals commonly include bradycardia, bradyarrhythmias, and hypotension, with other recognized adverse effects including pleural effusion, gingival hyperplasia, peripheral edema, gastrointestinal distress, hypothermia, central nervous system depression,

and electrolyte abnormalities[6]. While there are currently no consensus guidelines for the treatment of CCB toxicosis in human or veterinary medicine, several retrospective studies and case series have been published in the offering best practice recommendations[6–9]. A recent veterinary review on CCB toxicosis highlighted decontamination and cardiovascular optimization using fluids and vasoactive medications as the most important interventions. Therapeutic recommendations also included the use of glucagon or intravenous lipid emulsion as secondary options for refractory toxicoses, and other supportive therapies as needed[6].

An important therapeutic intervention that has resulted in improved patient outcomes over the last 15 years in human patients is hyperinsulinemic-euglycemic therapy (HIET), with multiple publications outlining its efficacy in the human literature[10–12]. HIET utilizes supraphysiologic doses of insulin, with human doses ranging from 0.5-2.0 U/kg/hour, and concurrent dextrose supplementation to maintain euglycemia[12]. In brief, blockade of the L-type calcium channels that result in the antihypertensive effect of CCBs also decreases the release of insulin from pancreatic beta cells and reduces glucose uptake by tissues by decreasing sensitivity to insulin, with concurrent vasodilation and hypoperfusion leading to negative inotropy. Increasing insulin availability encourages glucose utilization by the myocardium and suppresses phosphodiesterase III activity, leading to intracellular calcium influx and a positive inotropic effect[6]. Treatment with HIET is considered a first-line intervention in CCB toxicity in human patients[13]. There are limited reports of the use of HIET in CCB toxicity in clinical patients in veterinary medicine. There is one case report of survival after HIET was utilized for diltiazem toxicosis in one dog, and another report of HIET therapy utilized for amlodipine toxicosis in a cat, although HIET was discontinued after 3 hours due to refractory hypoglycemia[14,15]. There are also two animal model studies outlining efficacy of HIET for CCB toxicosis in anesthetized dogs[16,17]. To the authors' knowledge, this is the first report describing a protocol for HIET for the treatment of amlodipine toxicosis in the dog.

Case description

A 1-year-old spayed female mixed breed dog, weighing 14.8 kg, presented to the emergency service for evaluation of ataxia and lethargy approximately 48 hours after ingestion of at least 10 mg of amlodipine (at least a 0.7 mg/kg dose). The ingestion was not witnessed by the owner, but the dog had access to a bottle containing 8 tablets of 10 mg standard release amlodipine, of which one was missing, and half of another tablet had been chewed, resulting in a maximum exposure dose of ˜1 mg/kg. The dog reportedly displayed no adverse clinical signs for 24 hours after the potential ingestion, then developed lethargy, anorexia, vomiting, and ataxia in the next 24 hours. After consultation with a poison control center (Pet Poison Helpline, SafetyCall International, LLC), immediate veterinary care was recommended.

At presentation, the dog was hypothermic with a rectal temperature of 37.2°C (98.9°F), bradycardic (80 beats/min), tachypneic (52 breaths/min), and dull. The dog was weakly ambulatory and the physical exam was otherwise normal. Systolic blood pressure using a Doppler ultrasonographic device (Parks Medical Electronics, Inc.) was 65 mm Hg. Venous blood was obtained when the peripheral catheter was placed for a PCV/total solids and blood gas with electrolytes. Pertinent findings included a PCV of 54% and a total solids of 66 g/L, a mixed acid-base status, hypocapnia, hyponatremia, hyperkalemia, ionized hypocalcemia, hyperglycemia, hyperlactatemia, decreased bicarbonate, and azotemia (Table 1).

TABLE 1. Serial venous blood gas analysis.

	0 hours (8 PM)	4 hours	10 hours	18 hours	27 hours	36 hours	43 hou
pH	7.422	7.479	7.423	7.503	7.463	7.418	7.537
$PvCO_2$ (kPa)[mm Hg]	3.07 [23.1]	2.58 [19.4]	2.74 [20.6]	2.71 [20.4]	3.05 [22.9]	3.91 [29.4]	2.93 [2
PvO_2 (kPa) (mm Hg)	6.96 [52.3]	7.73 [58.1]	8.99 [67.6]	11.07 [83.2]	11.07 [83.2]	8.15 [61.3]	2.93 [2
SO_2 (%)	87.8	92.3	93.8	98.2	97.1	—-	—-
HCT (L/L)	47	45	47	43	45	43	43
Hemoglobin (mmol/L) [g/dL]	9.68 [15.6]	9.31 [15.0]	9.62 [15.5]	8.93 [14.4]	9.31 [15.0]	8.87 [14.3]	8.87 [1
Na (mmol/L)	123.3	121.6	121.0	121.6	126.8	128.7	125.0
K (mmol/L)	6.32	7.25	6.65	4.77	4.99	4.14	3.74

	0 hours (8 PM)	4 hours	10 hours	18 hours	27 hours	36 hours	43 hou
Cl (mmol/L)	—-	94.6	96.6	95.6	96.9	98.6	96.1
Ionized Ca (mmol/L)	1.07	1.02	1.28	1.17	1.38	1.40	1.17
Ionized Mg (mmol/L)	0.51	0.47	0.48	0.56	0.62	0.53	0.49
Glucose (mmol/L) [mg/dL]	13.3 [239]	11.0 [198]	6.7 [120]	4.8 [87]	3.7 [66]	1.9 [34]	7.0 [12
Lactate (mmol/L)	3.5	2.1	1.1	1.4	0.8	0.7	0.9
BUN (mmol/L) [mg/dL]	26.1 [73]	27.1 [76]	31.4 [88]	25.7 [72]	15.7 [44]	15.4 [43]	15.4 [4
Creatinine (µmol/L) [mg/dL]	344.8 [3.9]	380.2 [4.3]	309.5 [3.5]	238.7 [2.7]	194.5 [2.2]	159.2 [1.8]	159.2 [
HCO_3 (mmol/L)	15.2	14.5	13.6	16.1	16.6	19.2	18.9

Fluid therapy was initiated with a 20 ml/kg bolus of lactated Ringer's solution (Baxter Healthcare Corporation), given over 15 minutes, improving Doppler blood pressure to 110 mm Hg. Maropitant (Cerenia; Zoetis Inc) was also administered for the reported vomiting (1 mg/kg, IV q24). The dog was then admitted to the ICU for overnight care on a continuous infusion of lactated Ringer's solution (Baxter Healthcare Corporation) at 120 ml/kg/d to encourage diuresis, monitoring of temperature, pulse, and respiration, and every 2-hour monitoring of blood pressure. The first systolic blood pressure obtained in the ICU was 70 mm Hg. An additional 10 ml/kg lactated Ringer's solution fluid bolus was administered, with minimal effect as a recheck blood pressure was 80 mm Hg.

The consulting veterinarian at the poison control center (Pet Poison Helpline, SafetyCall International, LLC) was not confident that the reported amlodipine ingestion was likely to have caused all of the clinical signs given the timeline, but recommended monitoring electrolytes and blood pressure, fluid therapy at 120 ml/kg/day, and administering IV calcium as either bolus or CRI in case of persistent hypotension or bradycardia, with atropine also recommended for bradycardia.

Due to the persistent hypotension, continuous telemetry (Fukuda Denshi USA, Inc.) was initiated, and a 9.3 mg/kg bolus of 10% calcium gluconate (Fresenius Kabi) was administered over 10 minutes, followed by a continuous rate infusion (CRI) at 2.3 mg/kg/hr. Contemporaneously, a venous blood gas was obtained, revealing worsening hyponatremia, hyperkalemia, and azotemia (Table 1, hour 4). To address the hyperkalemia, the dog received 0.2 U/kg regular insulin (Humulin-R, Eli Lilly and Co.) IM, and the replacement fluid was changed to 0.9% sodium chloride (Vetivex; Dechra Pharmaceuticals) for the hyponatremia. Therapy with a 20% intralipid emulsion (ILE) (Clinoclipid; Baxter Healthcare Corporation) was initiated with a 1.5 ml/kg bolus followed by a 15 ml/kg infusion over 1 hour. Worsening respiratory rate and effort were noted, and the dog was placed in a climate-controlled oxygen cage (ICU 2100; Snyder Mfg. Co.) with an FiO2 of 40%. After initiation of intravenous calcium therapy, repeated blood pressure monitoring overnight ranged from 90-105 mm Hg, and the dog's demeanor was improved, eating small amounts of food and tolerating short walks. Similarly, a blood gas 4 hours after insulin showed improved hyperkalemia and hypocalcemia (Table 1, hour 10).

On the morning of the second day of hospitalization, the dog was subjectively overhydrated with serous nasal discharge and subcutaneous edema, tachypnea at 100 breaths/min with increased respiratory effort. A point-of-care ultrasound revealed moderate bilateral pleural effusion, severe bilateral B-lines (3+ in all fields), subjectively decreased cardiac contractility, and scant ascites. Weight had increased to 16.2 kg. In response to the hypervolemia, fluid therapy was discontinued. The dog was sedated with 0.1 mg/kg butorphanol (Torbugesic; Zoetis Inc) IV, a right-sided thoracocentesis was performed removing approximately 200 mL or 13 mL/kg of a straw-colored effusion, and furosemide (Salix; Merck Animal Health) was administered at 2 mg/kg IV. A chemistry panel about that time revealed azotemia, hyponatremia, hyperkalemia, hypochloremia, decreased bicarbonate, hyperphosphatemia, and an elevated anion gap (Table 2). A baseline cortisol was elevated at 16.1 ug/dL. In response to the hyperkalemia, terbutaline (Fresenius Kabi) was administered at 0.01 mg/kg IV. In response to the fluid intolerance, azotemia, and concern for poor cardiac output, the decision was made to initiate hyperinsulinemia-euglycemia therapy (HIET) approximately 16 hours after presentation, as detailed in Table 3. A central venous catheter (MILA International, Inc.) was

placed using the modified Seldinger technique as well as a continuous interstitial glucose monitor (FreeStyle Libre 2, Abbott) to allow for monitoring of interstitial glucose. Insulin (Humulin-R, Eli Lilly and Co.) was initially initiated at 0.1 U/kg/hr during placement of the central venous catheter and incrementally increased to 0.5 U/kg/hr over 12 hours. Supplemental dextrose was provided with a 5% solution of dextrose (50% dextrose, VetOne) in 0.9% saline (Vetivex; Dechra Pharmaceuticals) at 16 ml/kg/d, which was incrementally increased to a 15% solution over the next 12 hours. A 0.5 ml/kg bolus of 50% dextrose (VetOne) diluted 1:1 with 0.9% saline (Vetivex; Dechra Pharmaceuticals) was administered 6 hours after initiation of HIET in response to a blood sugar of 54 mg/dL. Repeated blood gas analysis after initiation of HIET showed improvement in azotemia and hyperkalemia (Table 1, hour 18). 10 hours after initiation of HIET, the dog developed recurrent hypotension at 60 mm Hg, and a norepinephrine (Levophed; Hospira, Inc.) CRI was started at a range of 0.1-0.5 µg/kg/min to maintain a systolic blood pressure of at least 90 mm Hg while increasing insulin and dextrose concentrations. Supplemental oxygen was increased to an FiO2 of 60% and 3 additional furosemide (Salix; Merck Animal Health) doses of 1, 1, and 2 mg/kg were administered overnight in response to worsening tachypnea. Serial point-of-care ultrasound every 4 hours after starting HIET revealed subjectively improved cardiac contractility with no evidence of worsening of pleural or abdominal effusion, but the B-lines were persistent.

TABLE 2. Serial biochemical analysis.

	Day 2	Day 4	Day 5	Reference ranges
Albumin (g/L) [g/dL]	28.3 [2.83]	24.6 [2.46]	25.1 [2.51]	26.2-39.1 [2.62-3.91]
BUN (mmol/L) [mg/dL]	39.3 [110]	26.1 [73]	26.8 [75]	2.5-9.6 [7-27]
Creatinine (µmol/L) [mg/dL]	188.3 [2.13]	122.0 [1.38]	120.3 [1.36]	53.1-132.6 [0.6-1.5]
Na (mmol/L)	117.0	122.8	121.2	141.9-150.6
K (mmol/L)	7.3	3.8	3.3	3.8-5.0
Cl (mmol/L)	85.6	84.9	84.7	107.8-117.1
Bicarbonate (mmol/L)	14	23	22	16-24
Ca (mmol/L) [mg/dL]	2.5 [10.0]	2.3 [9.1]	2.2 [8.8]	2.4-2.6 [9.7-10.4]
Phosphorous (mmol/L) [mg/dL]	2.9 [9.1]	1.6 [5.1]	1.4 [4.2]	0.7-1.5 [2.2-4.8]
Anion gap (mmol/L)	24.7	18.7	17.8	12.8-22.8

TABLE 3. Hyperinsulinemia-euglycemia therapy details.

Time, hours since initiation of HIET	Glucose (mmol/L) [mg/dL]	Insulin (U/kg/hr)	Dextrose concentration in 0.9% sa
0	7.5 [136]	0.1	5%
2	Not obtained	0.1	5%
4	6.4 [115]	0.2	10%
6	3.0 [54]	0.2	10%
8	3.3 [60]	0.2	12.5%
10	4.1 [74]	0.1	12.5%
12	3.6 [64]	0.1	15%
14	5.2 [94]	0.1	15%
16	5.3 [95]	0.1	15%
18	4.9 [88]	0.5	15%
20	Not obtained	0.5	20%
22	1.9 [34]	0.5	20%
24	6.4 [116]	–	20%
26	9.7 [174]	–	20%

On the morning of the third day of hospitalization, blood pressure had improved to 110 mm Hg and the norepinephrine CRI was able to be discontinued. A hypoglycemic seizure occurred approximately 22 hours after initiation of HIET, with a blood glucose of 34 (Table 1, hour 36). The seizure was terminated with the administration of a 0.5 ml/kg 50% dextrose (VetOne) bolus diluted 1:1 with 0.9% saline (Vetivex; Dechra Pharmaceuticals). Due to the continued improvement in electrolyte abnormalities on serial blood gas analysis as well as the hypoglycemic seizure, the decision was made to discontinue the insulin CRI and wean the dextrose solution. This was accomplished over the following 4 hours as the dog rapidly became hyperglycemic. At discontinuation, the dog's weight had decreased to 15.3 kg from 16.2 kg approximately 24 hours prior. Due to the persistent tachypnea and B-lines on point of care ultrasound, a 6-hour furosemide (Salix; Merck Animal Health) CRI at 0.5 mg/kg/hr was initiated, followed by bolus therapy at 1 mg/kg IV q6. An echocardiogram after completion of the CRI revealed no evidence of structural heart disease or congestive heart failure, and the observed fluid intolerance was believed to be most likely secondary to the bradycardia and hypotension associated with amlodipine toxicity.

The dog was hospitalized for 3 additional days and continued to improve daily. Furosemide was discontinued on the 4th day of hospitalization, and supplemental oxygen was discontinued on the 5th day of hospitalization. Capromorelin (Entyce®, Elanco) was instituted on the 5th day of hospitalization due to mild intermittent hyporexia, with improvement in appetite observed afterwards, avoiding nasogastric tube placement. The dog was discharged on day 6 with near complete resolution of biochemical abnormalities, and oral capromorelin (Entyce®, Elanco) for ongoing hyporexia. Follow up after approximately 9 months revealed that the dog was doing well with no reported long-term adverse effects, although no repeated bloodwork was available for review.

Discussion

To the authors' knowledge, this is the first case report describing the use of HIET therapy to treat amlodipine toxicosis in a dog. As reported in the human literature, this case report suggests that HIET is an effective means of controlling the cardiovascular collapse associated with amlodipine toxicosis in the dog. Current dosing of HIET has as of yet not been well defined in human literature, with recommendations for initial dose ranging from 0.3-1.0 U/kg/hr in various reports and a generally acknowledged ceiling of 10 U/kg/hr, although a report of a dose of 21.8 U/kg/hr secondary to an administration error was tolerated by the patient and led to survival to discharge[18,19]. Similarly, response times are variable. One report identified improvements in blood pressure approximately 30 minutes after starting HIET, but other reports have shown times up to four hours[7,10,18]. As the decision to initiate HIET in this dog was based on the azotemia and fluid intolerance noted on the morning of the second day of hospitalization as opposed to refractory hypotension as previously described in canine patients, response to therapy is harder to define, especially given the dog's development of hypotension during therapy[14]. However, as noted by serial blood gas analysis, the azotemia and lactate concentrations improved during HIET, suggestive of improved cardiac output. Similarly, the dog experienced a reduction in weight on HIET, suggestive of mobilization of previously administered fluids. In this sense, the authors' goals for usage of HIET are in line with a human toxicology group recommending the use of HIET to maintain cardiac output and tissue perfusion as defined by clinical parameters such as mental status and urinary output as opposed to a target MAP[20]. The dog's development of hypotension is unexpected but may be reflective of an ineffective insulin dose, and more aggressive titration may be required. However, insulin has also been shown to enhance the expression of endothelial nitric oxide synthase causing vasodilation, and it is not uncommon for patients with CCB toxicosis to still require vasoactive medications[18,21]. Indications for discontinuation of HIET are also not well defined, but generally the recommendation is to discontinue once the patient is hemodynamically stable[18]. This factored into the decision to discontinue HIET in this dog, as HIET was discontinued when the patient was normotensive without norepinephrine; although part of the reason for discontinuation was the development of a hypoglycemic seizure.

The dog also experienced several less frequently identified adverse effects from the amlodipine overdose, including the development of hyponatremia, pleural effusion, and suspected non-cardiogenic pulmonary edema, but was able to make a full recovery. Due to the atypical clinical presentation, other differentials such

as congenital or acquired cardiac disease were considered, but with a structurally normal heart and a drug bottle visibly damaged by teeth, amlodipine toxicosis was considered most likely. The remainder of the dog's clinical and laboratory findings, such as hyperglycemia, mild ionized hypercalcemia, and hypotension, are associated with CCB toxicosis[9]. Hyponatremia has previously been reported to be associated with HIET in humans, but the development of hyponatremia preceded HIET in this case[22]. CCBs are natriuretic, with increased tubular excretion and inhibition of sodium reabsorption[6]. While the dog's azotemia and hyperkalemia are not commonly associated with CCB toxicosis, they have been previously reported, likely secondary to prolonged hypotension and decreased renal perfusion[6]. Pleural effusion has been previously reported in association with amlodipine toxicosis at levels thought to be therapeutic, although the mechanism is unknown, and right sided heart failure secondary to a concomitant decrease in systolic function associated with CCB toxicosis cannot be ruled out[5]. While financial constraints prevented full evaluation of the extent of the dog's pulmonary disease with radiographs, based on response to therapy and echocardiographic assessment, it is most likely that the dog's respiratory changes were purely secondary to relative volume overload and decreased cardiac output associated with amlodipine toxicosis.

While relatively novel in veterinary medicine, HIET has the potential to significantly improve patient outcomes. In human medicine, published fatality rates for amlodipine toxicosis range from 38-50%[11,23,24]. Given the significant improvement in cardiovascular status associated with HIET therapy in the literature, it should be part of the standard of care for canine patients unresponsive to traditional therapeutic interventions or those patients who present with profound clinical signs[18,20]. The decision for a gradual increase in the insulin dose was made empirically to balance the potential for adverse effects of hyperinsulinemia with the improved cardiovascular status; however, this dog may have benefitted from more aggressive therapy. Therefore, the authors recommend initiating insulin at 0.3 U/kg/hr with titration up to 1 U/kg/hr as needed for improvement of hemodynamic status, which has been previously described in dogs[14]. Additionally, due to concern for the dog's fluid intolerance, dextrose support was achieved using lower fluid rates but higher concentrations of dextrose, which may have predisposed to the development of hypoglycemia. The decision to use a continuous interstitial glucose monitor (FreeStyle Libre 2, Abbott) was made to ease technical demands during therapy but may have contributed to delayed recognition of the patient's hypoglycemia and subsequent seizure. While frequently used for critically ill patients in human and veterinary medicine, continuous interstitial glucose monitors have a lag time of 15-20 minutes, and may not be the best choice for monitoring in patients receiving HIET[25,26]. Hypoglycemia was the primary indication for discontinuation of HIET in another veterinary case report[15]. As such, the authors recommend blood glucose monitoring during therapy on at least an hourly basis with consideration for repeated checking sooner after adjustments in insulin dosage, in line with human recommendations[12,13,18].

Conclusion

This case report describes the use of HIET to treat cardiovascular abnormalities associated with amlodipine toxicosis. While the strongest indication for HIET is refractory hypotension in the presence of CCB toxicosis, this case shows that other adverse effects of CCB toxicosis may also show improvement due to the increased cardiovascular support provided by HIET.

Recommendations for the use of HIET for amlodipine toxicosis exist in both human and veterinary literature, but there are no currently published dose recommendations in the veterinary literature. This case describes the successful deployment of a protocol for HIET in dogs affected by amlodipine toxicosis. While potential complications may occur, HIET is an effective treatment for amlodipine toxicosis, and should be considered as first line therapy in patients with cardiovascular collapse or other severe adverse effects refractory to conventional therapy. Clinical trials are necessary to further evaluate the benefits of HIET, and further investigation into the optimal dosing and monitoring strategy for HIET is necessary to help minimize the risk of associated complications.

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Connor Ellis: Writing – original draft

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