

Approaches to diagnosing and treating hypoglycaemic patients

Author : Laura Cole, Dominic Barfield

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ABSTRACT

Hypoglycaemia is a common presentation in the emergency setting. After a review of normal glucose homeostasis, the clinical signs of hypoglycaemia are discussed. Methods of detection of hypoglycaemia are highlighted, including the pitfalls of point of care analysers when compared to laboratory measurement.

The review discusses the differential diagnoses for hypoglycaemia, emergency management of hypoglycaemia and second-line treatment. Further investigations are briefly discussed to help determine the underlying cause. Two case examples of hypoglycaemia are detailed to highlight the article's key points.

Hypoglycaemia is a life-threatening complication of a multitude of diseases.

Prompt recognition, treatment and diagnosis of the underlying cause is invaluable for a successful management of patients presenting with hypoglycaemia.

Normal glucose homeostasis



Figure 1. Example of a bedside glucometer.

To understand the mechanisms by which hypoglycaemia can develop, an appreciation of normal glucose homeostasis is required. Glucose is the body's key source of energy and the brain has an obligate requirement for it. Under normal conditions, glucose is produced as a result of breakdown of dietary carbohydrates, proteins and fats.

During periods of fasting, the liver is the sole producer of glucose via gluconeogenesis – the process by which glucose is synthesised from non-carbohydrate precursors – and glycogenolysis, which is the breakdown of glycogen.

Insulin is the predominate hormone regulating blood glucose levels. Insulin promotes the uptake of glucose into cells, primarily those of muscle and adipose tissue, and encourages the liver to convert more glucose into glycogen. Plasma insulin concentrations fall to lower levels in fasting states.

In low glucose concentration states, a number of hormonal responses exist in an attempt to safeguard the blood glucose level – rapid increase in adrenaline and glucagon, and, to a lesser extent, cortisol and growth hormone.

Adrenaline increases hepatic gluconeogenesis and has a lipolytic effect on adipose cells. It also stimulates glucagon production while inhibiting insulin release. Glucagon directly increases hepatic gluconeogenesis and glycogenolysis.

Growth hormone and cortisol have a predominant effect in the periphery, blocking peripheral glucose use (Leifer and Peterson, 1984). The effect of adrenaline and glucagon is short-lived, whereas the action of cortisol and growth hormone is delayed, but continues for hours to days (Davidson, 1981).

Clinical signs

Panel 1. Agonist definitions

Reduced substrate for gluconeogenesis

- Reduced intake:
 - – Neonatal and juvenile (often toy breed) hypoglycaemia*
- – Prolonged starvation
- Increased consumption:
 - – Sepsis*
 - – Infection (parvovirus, *Babesia* species, *Bartonella* species)
 - – Extreme exercise – hunting dog hypoglycaemia
 - – Paraneoplastic
 - – Pregnancy

Decreased hepatic gluconeogenesis

- Severe hepatic disease*
- Glycogen storage disease
- Hypoadrenocorticism*
- Counter-regulatory hormone deficiency; growth H/glucagon/ thyroid/catecholamines
- Renal failure
- Cardiac disease

Excessive insulin or insulin-like factors

- Iatrogenic insulin overdose*
- Oral hypoglycaemics; sulfonylureas (glipizide, chlorpropamide).
- Pancreatic beta cell neoplasia (insulinoma)*
- Extra-pancreatic tumour; hepatoma, hepatocellular carcinoma, leiomyoma, leiomyosarcoma, pulmonary carcinoma, mammary carcinoma, oral melanoma, haemangiosarcoma, lymphoma

- Beta-blockers
- Toxicity: xylitol*, oleander extract, jerky treats

Artefactual

- Delayed serum separation
- Polycythemia
- Leukocytosis

Adapted from Koenig (2009). *Indicates the most common causes.

Clinical signs of hypoglycaemia are variable, dependant on the rate of fall in glucose, the lowest blood glucose reading and the duration of hypoglycaemia.

When blood glucose drops slowly over time, the body adapts to these lower concentrations and, therefore, inappropriately mild clinical signs associated with a severe hypoglycaemia should alert the clinician to a chronic process.

Clinical signs of hypoglycaemia are usually not apparent until the blood glucose is less than 2.5mmol/L.

Clinical signs can be attributed to the increased sympathetic tone in response to hypoglycaemia and the effect of reduced glucose supply and subsequent cerebral adenosine triphosphate to the brain; neuroglycopenia. Adrenergic responses predominate in the acute stage, leading to tachycardia, vocalisation and tremors. Puppies and kittens have inefficient counter regulatory hormone release and, therefore, these early signs are usually lacking.

Neuroglycopenia results in mental dullness and can progress to collapse, seizures and coma. The initial phase of neuronal damage occurs within minutes and can progress to neuronal death through necrosis or apoptosis, even if glucose and glycogen stores return to normal levels (Loose et al, 2008).

Peripheral polyneuropathies have also been reported in some patients presenting with hypoglycaemia, resulting in paresis or paralysis. This is thought to occur as a result of glucose-mediated disturbances in the neurons. Despite no distinct correlation existing between duration and severity of hypoglycaemia and occurrence or severity of the polyneuropathy, clinical signs have been shown to resolve in some cases when euglycaemia was restored (Schrauwen et al, 1996).

In the author's experience, somewhat counter-intuitively, sinus bradycardia and circulatory collapse has been associated with non-septic hypoglycaemia and has been described in the veterinary and human literature.

This is suspected to occur as a result of central activation of the autonomic system – the parasympathetic, as well as sympathetic, nervous system (Pollack et al, 1996; Little, 2005).

These signs improved dramatically once the patient receives glucose supplementation.

Diagnosis

Hypoglycaemia is generally accepted as blood glucose concentrations are less than 3.4mmol/L (Feldman et al, 2015). Bedside glucometers (**Figure 1**) allow for rapid reliable diagnosis of hypoglycaemia on as little as 0.3ul of whole blood. Haemoconcentration can falsely lower the blood glucose when measured by point of care analysers and a low haematocrit falsely increases glucose measurements (Paul et al, 2011).

Laboratory diagnosis requires sample collection in fluoride tubes. Fluoride has the ability to stop enzymatic activity of the glycolysis pathway and, therefore, minimises the risk of artefactual hypoglycaemia.

However, this doesn't prevent loss of glucose in the first 30 to 60 minutes after blood collection (Chan et al, 1989).

Differentials of hypoglycaemia

Normoglycaemia requires an appropriate substrate for gluconeogenesis, a liver with glycogenolytic and gluconeogenic properties, and a balance of hormones that regulate glucose concentrations. From this, causes of hypoglycaemia can be categorised (**Panel 1**).

Hypoglycaemia as a result of starvation only occurs in severely malnourished individuals.

More common is toy breed hypoglycaemia, usually seen in toy breed puppies less than six months of age, as a result of a reduction in the supply of gluconeogenic substrate. This is usually precipitated by stress or fasting and responds quickly to supplemental glucose. Recurrent hypoglycaemia would warrant further investigations of other underlying causes (Chastain, 2001).

Hunting dog hypoglycaemia is seen in lean working dogs and thought to occur as a result of prolonged extreme exercise resulting in a depletion of liver glycogen stores in the face of increased glucose use. Infection is an often overlooked, but important, cause of hypoglycaemia.

Septic patients may have an initial stress hyperglycaemic phase, but there appears to be a

secondary hypoglycaemic phase where glucose production is suppressed and excessive glucose use occurs in the periphery (Chan, 2015). This can also be seen in parvoviral enteritis and has been documented as a complication of virulent canine babesiosis and bartonella infection (Keller et al, 2004; Breitschwerdt et al, 2014).

The liver is responsible for gluconeogenesis and glycogenolysis. The liver has a tremendous capacity to regenerate and, therefore, hypoglycaemia only occurs with severe liver dysfunction, such as a portosystemic shunt or hepatic cirrhosis. A commonly reported cause of hypoglycaemia in young and middle-aged dogs is hypoadrenocorticism. A deficiency in cortisol results in impaired gluconeogenesis and impaired glucose production.

Cardiac disease and renal failure are uncommon causes of hypoglycaemia, but occur as a result of reduced hepatic glycogen, deficiency of precursors of gluconeogenesis and impaired renal insulin degradation (Arem, 1989).

Insulin is produced usually only in response to feeding to remove glucose from circulation. However, excessive production of insulin or insulin-like factors occurs in a variety of pathological states and can result in hypoglycaemia. The most severe obvious cause is an insulinoma – a tumour of beta pancreatic cells. Other non-beta cell neoplasms that cause hypoglycaemia include hepatomas and hepatic carcinomas. These neoplasms cause hypoglycaemia via secretion of insulin-like peptides and accelerated consumption of glucose by the tumour cells (Koeing, 2009).

In dogs, xylitol, an artificial sweetener used in chewing gum, can cause a mass release in insulin and subsequent hypoglycaemia independent of liver function (Dunayer, 2004). Hypoglycaemia has also been reported in dogs associated with oleander extract toxicity, dried chicken jerky treats and alpha lipoic acid (Feldman et al, 2015).

When interpreting the significance of hypoglycaemia, it is important to bear in mind the effect of polycythemia and leukocytosis on glucose levels. Hypoglycaemia can occur secondary to increased metabolism of glucose by the erythrocytes and leukocytes.

Emergency management

Drug	Dosage and route of administration	Comment
Dextrose	0.5ml/kg to 1ml/kg of 50 per cent dextrose followed by 2.5 per cent to 5 per cent dextrose solution.	2.5 per cent solution: 50ml of 50 per cent dextrose to 950ml of 0.9 per cent saline 5 per cent solution: 100ml of 50 per cent dextrose to 900ml of 0.9 per cent saline.
Glucagon	Bolus 50ng/kg IV or SC followed by constant rate infusion.	
Glucocorticoids	Dexamethasone 0.1 mg/kg to 0.2mg/kg IV. Prednisolone 0.1 mg/kg to 0.5mg/kg by mouth.	Use in management of hypoadrenocorticism in the emergency setting. Contraindicated in infection induced hypoglycaemia.

Adapted from Koenig (2009).

Table 1. Emergency management of hypoglycaemia. Adapted from Koenig (2009).

Traditionally treatment of iatrogenic insulin-induced hypoglycaemia is limited itself to administration of dextrose or glucose transmucosally or intravenously in the hospital. The author uses 0.5ml/kg to 1ml/kg 50% dextrose diluted (to 10% or less solution) given slowly intravenously. The clinical signs should resolve rapidly on administration of glucose.

The goal of emergent therapy is to eliminate the neuroglycopenic signs. After initial treatment and the patient is able to, it should be offered regular food or be started on a glucose infusion. A 2.5% or 5% dextrose solution can be made adding 50% dextrose to isotonic crystalloid fluid (**Table 1**).

Blood glucose should be monitored closely to ensure adequate supplementation is administered. Patients with an insulinoma should not receive excessive glucose supplementation to minimise the rebound release of insulin and worsening hypoglycaemia – the aim of therapy is to control the neurological signs, not to normalise the patient's blood glucose levels.

In these patients, the use of glucagon may be used cautiously to maintain normoglycaemia. Studies in animals have shown the effectiveness of glucagon administered subcutaneously, as well as intravenously in dogs (Zeugswetter et al, 2012).

Glucocorticoids promote gluconeogenesis, as well as having insulin antagonism effects. They may help stabilise patients with excessive insulin or insulin-like factors, such as in certain neoplastic conditions, as well as those patients with hypoadrenocorticism. However, glucocorticoids are rarely indicated in the emergency setting and are contraindicated in cases of infection.

Diagnosics

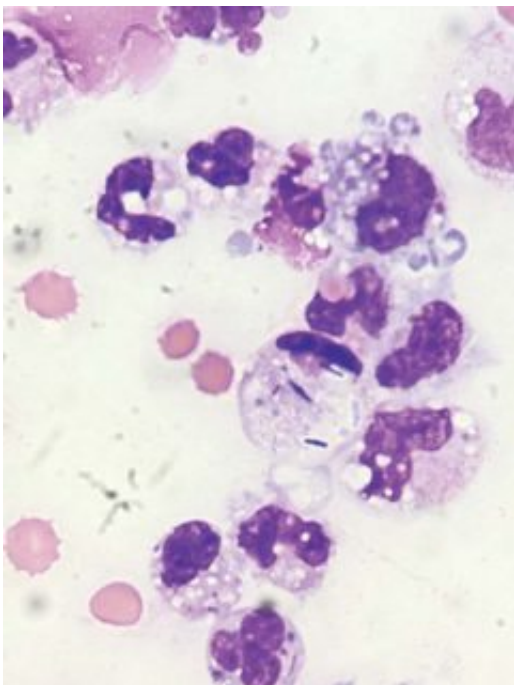


Figure 2. Fluid cytology.

Emergency diagnostics is predominantly required to rule out sepsis as a cause of the hypoglycaemia. In these patients, early detection of the septic foci is paramount to achieve rapid source control and allow for early appropriate antibiotic therapy. Abdominal and thoracic ultrasound adapted from use in trauma patients can be used in the emergency setting to allow rapid detection and sampling of free fluid (McMurray et al, 2016).

A glucose concentration difference between plasma and peritoneal effusion greater than 2mmol/L is suggestive of a septic effusion (Koeing and Verlander, 2015). This can be used alongside identification of intracellular bacteria on in-house cytology to support a diagnosis of septic peritonitis (**Figure 2**).

Basic emergency blood profile to allow assessment of electrolytes and protein levels is also important. This could help support a diagnosis of hypoadrenocorticism. Although not an emergency diagnosis, a serum sample should be taken for an insulin assay prior to administration of glucose.

A diagnosis of insulinoma can be established by demonstrating inappropriately high levels of insulin associated with a laboratory documented hypoglycaemia (Feldman et al, 2015).

Further work-up

Biochemistry will allow for assessment of markers of liver function. Low urea, total solids and hypocholesterolaemia should alert the clinician to the possibility of liver dysfunction. A haematology profile, alongside electrolyte analysis, will help rule hypoadrenocorticism in or out. However, a basal cortisol or adrenocorticotrophic hormone stimulation test should be used to confirm diagnosis.

Thoracic radiography may be performed in cases of suspected aspiration pneumonia. Specialist ultrasound or advanced imaging will likely be required for detection of insulinoma and other neoplasms. Hypoglycaemia is a common presentation that requires rapid treatment. However, a range of conditions can lead to hypoglycaemia – some of which will affect how the patient is managed in the acute stages. Therefore, the clinician should have a good grasp of the possible causes of hypoglycaemia and approach to diagnosis.

Case examples

Two case examples are detailed in **Panels 2 and 3**.

Panel 2: Case 1

Signalment: three-year-old male, neutered crossbreed dog

History: three days of anorexia and lethargy

Physical examination: the patient was moderately obtunded. It had dry mucus membranes with a prolonged capillary refill, heart rate 120bpm and mild cranial abdominal pain

Emergency diagnostics: no free fluid identified on patient side thoracic and abdominal ultrasound

Emergency blood database:

- Glucose 1.2mmol/L
- Sodium 138mmol/L (140mmol/L and 153mmol/L)
- Chloride 111mmol/L (106mmol/L to 120mmol/L)
- Potassium 5.0mmol/L (3.6mmol/L to 4.6mmol/L)
- Urea 19.5mmol/L (3mmol/L to 10mmol/L)
- Creatinine 160mmol/L (50mmol/L to 140umol/L)
- Sodium-potassium ratio 27.6

Emergency treatment: 1ml/kg 50 per cent glucose, then 5 per cent dextrose solution

Adrenocorticotrophic hormone stimulation test – cortisol post-stimulation: greater than 27.6nmol/L

Interpretation: hypoadrenocorticism

Panel 3: Case 2

Signalment: 10-year-old male, neutered Labrador retriever

History: progressive exercise intolerance, lethargy and weakness

Physical examination: the patient was bright and responsive, hydration was adequate, heart rate was 96bpm with synchronous pulses, abdominal palpation was unremarkable, and pelvic limb paresis and delayed conscious proprioception was apparent

Emergency diagnostics: no free fluid identified on patient side ultrasound

Emergency blood profile: unremarkable except for hypoglycaemia (1.5mmol/L). Blood also collected in fluoride tube and serum tube for laboratory assessment of hypoglycaemia and insulin assay

Emergency treatment: 0.5ml/kg 50 per cent glucose infusion and then 2.5 per cent glucose infusion

Insulin assay: insulin greater than 300U/ml

CT: consistent pancreatic neoplasia

Interpretation: insulinoma

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